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(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Biphenyl Derivatives, Pharmaceutical Compositions Containing These Compounds and Processes for Preparing Them

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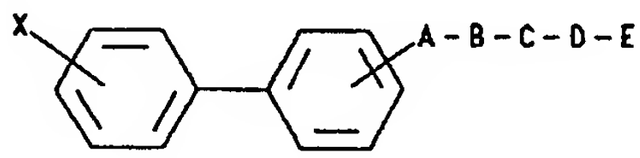
Abstract

Biphenyl derivatives

The invention relates to biphenyl derivatives of formula I



(I)

(wherein A to E and X are defined as in claim 1) and the stereoisomers and salts thereof, compounds which have valuable therapeutic properties, and in particular aggregation-inhibiting effects.

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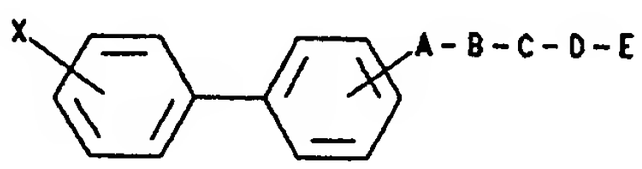
Biphenyl derivatives

The invention relates to biphenyl derivatives and to pharmaceutical compositions containing them and to their use in human and veterinary medicine.

It has been found that certain novel biphenyl compounds have valuable pharmacological properties; in addition to having an inhibitory effect on inflammation and bone degradation, they have, in particular, antithrombotic, antiaggregatory and tumour- or metastasis-inhibiting effects.

Thus viewed from one aspect the invention provides compounds of formula I



(I)

(wherein
one of the rings of the biphenyl moiety may be mono- or disubstituted by a group R_1 and the other may be mono- or disubstituted by a group R_2,

R_1 and R_2, which may be identical or different, each represents a halogen atom or a naphthyl, alkyl, hydroxy, trifluoromethyl, amino, nitro, alkoxy, alkylsulphenyl, alkylsulphinyl, alkylsulphonyl, alkylcarbonylamino, N-alkyl-alkylcarbonylamino, arylcarbonylamino, N-alkyl-arylcarbonylamino, alkylsulphonylamino or N-alkyl-alkylsulphonylamino group or an arylsulphonylamino or N-alkyl-arylsulphonylamino group wherein the aryl moiety may contain a phenyl ring optionally mono-, di- or trisubstituted by halogen atoms or hydroxy, amino, alkyl, alkoxy, alkylsulphenyl, alkylsulphinyl,

alkylsulphonyl, alkylcarbonylamino and alkylsulphonylamino groups;

X represents a cyano group or an amino, aminoalkyl, amidino, guanidino or guanidinoalkyl group, wherein one of the hydrogen atoms at one of the nitrogen atoms may be replaced by a hydroxy, amino or cyano group, by a C_{1-3}-alkoxy group, by a C_{1-4}-alkyl group, by a C_{2-5} (alkoxycarbonyl) group, by a phenyl(C_{1-3}alkoxy)-carbonyl group, or by a phenyloxycarbonyl, benzoyl, (C_{1-3}alkyl)-carbonyl or phenyl(C_{1-3}alkyl)carbonyl group, wherein any phenyl group is optionally mono- or disubstituted by a group R_1 or R_2;

A represents a bond, an oxygen or sulphur atom or an $-NR_3-CO-$, $-CO-NR_3-$, $-NR_4-$, $-SO-$, $-SO_2-$, $-CO-$, $-SO_2-NR_3-$, $-NR_3-SO_2-$, $-NR_3-CO-NR_3-$ or $-NR_3-SO_2-NR_3-$ group;

B represents a bond, a straight-chained or branched C_{1-6}-alkylene group which may be mono- or polyunsaturated, although a double bond may not be directly linked to an oxygen, sulphur or phosphorus atom of groups A, C or E and a triple bond may not be directly linked to a heteroatom of groups A, C or E, or B may represent a C_{3-7}-cycloalkylene group or a phenylene or naphthylene group which may be mono-, di- or trisubstituted in the aromatic nucleus by halogen atoms, amino, hydroxy, C_{1-3}-alkyl or C_{1-3}-alkoxy groups;

C represents a bond, a $-CO-$, $-CO-NR_3-$, $-CO-NR_3-(CH_2)_n-R_5CR_6-$, $-CO-NR_3-(CH_2)_n-NR_5-$ or $-CO-NR_3-(CH_2)_n-CR_5=CH-$ group, or, if a heteroatom of group A is not bound to the same carbon atom of group B as is group C, C may represent an oxygen or sulphur atom, an $-SO-$, $-SO_2-$, $-NR_4-$, $-NR_3-CO-$ or $-NR_3-(CH_2)_n-CHR_5-$ group, although an oxygen or sulphur atom of group C cannot directly follow an oxygen or sulphur atom or a $-CO-$

group of group A and an oxygen atom or a sulphenyl or sulphinyl group of group C cannot directly follow a nitrogen atom of group A and a -CO- group of group C cannot directly follow an oxygen or sulphur atom or a $-CO-NR_3-$ group of group A;

D represents a bond, a straight-chained or branched C_{1-4}-alkylene group which may be mono- or polyunsaturated, although a double bond may not be bound directly to an oxygen, sulphur or phosphorus atom of groups A, C or E or to a triple bond of group B and a triple bond may not be directly linked to a heteroatom of groups A, C or E or to a double or triple bond of group B, or D may represent a phenylene or (C_{1-3}-alkylene)phenylene group optionally mono-, di- or trisubstituted in the phenyl nucleus by halogen atoms, amino, hydroxy, C_{1-3}-alkyl or C_{1-3}-alkoxy groups;

E represents a carboxy, sulpho, phosphono, 5-tetrazolyl, O-(C_{1-3}alkyl)-phosphono or $(R_3)_2NCO-$ group or a C_{2-6}-(alkoxy-carbonyl) group wherein the alkoxy moiety may be substituted in the 1-, 2- or 3-position by a phenyl group (itself optionally mono- or disubstituted by groups R_1 or R_2) or by a pyridyl group or in the 2- or 3-position by a pyrrolidino, piperidino, hexamethyleneimino, 2-oxo-1-pyrrolidinyl, morpholino, thiomorpholino, 1-oxido-thiomorpholino or 1,1-dioxidothiomorpholino group or by a piperazino group itself optionally substituted in the 4-position by a group R_5;

n represents the number 0, 1 or 2,

R_3 represents a hydrogen atom or an optionally phenyl-substituted C_{1-3}-alkyl group, wherein the phenyl group is itself optionally mono- or disubstituted by groups R_1 or R_2;

R_4 represents a hydrogen atom, an optionally phenyl-

substituted C_{1-3}-alkyl group, a formyl group, a carbonyl or sulphonyl group substituted by a C_{1-3}-alkyl group, by a phenyl(C_{1-3}-alkyl) group or by a phenyl group, wherein the phenyl groups may be mono- or disubstituted by groups R_1 or R_2; and

R_5 represents a hydrogen atom or a C_{1-3}-alkyl group or a -CO-NR_3-(C_{1-3}-alkylene)-phenyl group in which the phenyl group may be mono- or disubstituted by groups R_1 or R_2, or if group C is substituted by the groups R_3 and R_5, then R_5 together with R_3 may represent a C_{2-4}-alkylene group; and

R_6 represents a hydrogen atom or a hydroxy, carboxyalkyl or alkoxycarbonylalkyl group;

whilst at least one of the groups A, B, C and D does not represent a bond, group E cannot directly follow a heteroatom of groups A or C and, if X represents an aminoalkyl group, the shortest distance between the NH_2 group and group E is at least 12 bonds, and each alkyl, alkylene or alkoxy moiety unless otherwise specified contains 1 to 3 carbom atoms) and the stereoisomers thereof, including mixtures thereof and the salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases.

Preferred compounds according to the invention include compounds of formula I wherein one of the rings of the biphenyl moiety may be substituted by R_1 and the other may be substituted by R_2 where R_1 and R_2, which may be identical or different, each represents a fluorine, chlorine or bromine atom, or an alkyl, hydroxy, trifluoromethyl, amino, nitro, alkoxy, alkylsulphenyl, alkylsulphinyl, alkylsulphonyl, alkylcarbonylamino, benzoylamino, alkylsulphonylamino or phenylsulphonylamino group,

or wherein one of the rings of the biphenyl moiety may

be disubstituted by R_1 and the other by R_2 where R_1 and R_2, which may be identical or different, each represents a C_{1-3}-alkyl group or a chlorine or bromine atom;

X represents a cyano group, an amino(C_{1-3}-alkyl), amino, amidino or guanidino group wherein one of the hydrogen atoms at one of the nitrogen atoms in these groups may be substituted by an amino group, by a C_{1-4}-alkyl group, by a C_{1-3}-alkoxy, by a C_{2-5}(alkoxycarbonyl) group, or by a benzyloxycarbonyl, 1-phenylethoxycarbonyl, 2-phenylethoxycarbonyl or phenyloxycarbonyl group;

A represents a bond, an oxygen or sulphur atom or an $-NR_3-CO-$, $-CO-NR_3-$, $-NR_4-$, $-SO-$, $-SO_2-$, $-CO-$, $-SO_2-NR_3-$, $-NR_3-CO-NR_3-$ or $-NR_3-SO_2-NR_3-$ group;

B represents a bond, a straight-chained or branched C_{1-6}-alkylene group or a C_{3-5}-alkenylene or C_{3-5}-alkynylene group although a double bond may not be linked directly to an oxygen, sulphur or phosphorus atom of groups A, C or E and a triple bond may not be directly linked to a heteroatom of groups A, C or E, or B may represent a cyclohexylene or phenylene group;

C represents a bond, a $-CO-NR_3-$, $-CO-NR_3-(CH_2)_n-R_5CR_6-$, $-CO-NR_3-(CH_2)_n-NR_5-$, or $-CO-NR_3-(CH_2)_n-CR_5=CH-$ group, or, if a heteroatom of group A is not bound to the same carbon atom of group B as is group C, C may also represent an oxygen or sulphur atom or an $-SO-$, $-SO_2-$, $-NR_4-$, $-NR_3-CO-$ or $-NR_3-(CH_2)_n-CHR_5-$ group although generally an oxygen or sulphur atom of group C cannot directly follow an oxygen or sulphur atom or a $-CO-$ group of group A, and an oxygen or sulphenyl or sulphinyl group of group C cannot directly follow a nitrogen atom of group A, and a $-CO-$ group of group C cannot directly follow an oxygen or sulphur atom or a $-CO-NR_3-$ group of group A;

D represents a bond, a straight-chained or branched C_{1-4}-alkylene group or a phenylene or (C_{1-3}-alkylene)phenylene;

E represents a carboxy, sulpho, phosphono, 5-tetrazolyl, O-(C_{1-3}alkyl)-phosphono or $(R_3)_2NCO$- group or a C_{2-5}(alkoxy-carbonyl) group wherein the alkoxy moiety may be substituted in the 1-, 2- or 3-position by a phenyl or pyridyl group or the alkoxy moiety may be substituted in the 2- or 3-position by a 2-oxo-1-pyrrolidinyl, morpholino, thiomorpholino or 1-oxido-thiomorpholino group;

n represents the number 0, 1 or 2;

R_3 represents a hydrogen atom or a C_{1-3}-alkyl group;

R_4 represents a hydrogen atom, a C_{1-3}-alkyl group or a carbonyl or sulphonyl group substituted by a C_{1-3}-alkyl group or by a phenyl group;

R_5 represents a hydrogen atom or a C_{1-3}-alkyl group or a $-CO-NR_3-(C_{1-3}$-alkylene)-phenyl group wherein the phenyl moiety may be substituted by one or two C_{1-3}-alkoxy groups or, if the group C is substituted by the groups R_3 and R_5, then R_5 together with R_3 may represent a C_{2-4}-alkylene group; and

R_6 represents a hydrogen atom or a hydroxy, carboxyalkyl or alkoxycarbonylalkyl group;

at least one of the groups A, B, C and D does not represent a bond, group E cannot directly follow a heteroatom of group A or C and, if X represents an aminoalkyl group, the shortest distance between the NH_2 group and group E is at least 12 bonds, and each alkyl, alkylene or alkoxy moeity unless otherwise specified

contains 1 to 3 carbon atoms;

and the stereoisomers thereof, including the mixtures and the salts thereof.

Particularly preferred compounds according to the invention include compounds of formula I wherein

the phenyl group linked to the group X is substituted by a fluorine, chlorine or bromine atom;

the phenyl ring linked to the group A is substituted by a fluorine or chlorine atom or by a hydroxy, methoxy, trifluoromethyl, methylsulphenyl, methylsulphinyl, methylsulphonyl, nitro, amino, acetylamino, benzoylamino, methanesulphonylamino or benzenesulphonyl-amino group or the phenyl ring linked to group A is substituted by one or two methyl groups or by one or two bromine atoms;

X represents an aminomethyl, amidino or guanidino group wherein a hydrogen atom at one of the nitrogen atoms may be replaced by a C_{1-4}-alkyl group, or by a methoxycarbonyl, ethoxycarbonyl or benzyloxycarbonyl group;

A represents a bond, an oxygen or sulphur atom or an $-NH-CO-$, $-NCH_3-CO-$, $-CO-NH-$, $-CO-NCH_3-$, $-NCH_3$, $-SO-$, $-SO_2-$, $-SO_2-NH-$, $-SO_2-NCH_3-$, $-CO-$, $-NH-CO-NH-$, $-NH-SO_2-NH-$ or $-NCH_3-CO-NCH_3-$ group;

B represents a bond, a straight-chained or branched C_{1-5}-alkylene group, a straight-chained or branched C_3-alkenylene group in which the double bond cannot be directly linked to an oxygen, sulphur or phosphorus atom of groups A, C or E, or B represents a cyclohexylene or phenylene group;

C represents a bond, a -CO-NH-, -CO-NCH_3-, -CO-NH-$(CH_2)_2$-CH(CH_2-COOH)-, -CO-NCH_3-$(CH_2)_2$-CH(CH_2-COOH)-, -CO-NH-$(CH_2)_2$-CH(CH_2-$COOCH_3$)-, -CO-NCH_3-$(CH_2)_2$-CH(CH_2-$COOCH_3$)-, pyrrolidinylene-N-carbonyl, piperidinylene-N-carbonyl or piperazinylene-N-carbonyl group, a 4-methanylylidene-piperidinocarbonyl group wherein the group -D-E is bound to the methanylylidene moiety, a 4-hydroxy-4-piperidinylene-N-carbonyl, 4-carboxymethyl-4-piperidinylene-N-carbonyl or 4-methoxycarbonylmethyl-4-piperidinylene-N-carbonyl group wherein the group -D-E is bound to the 4-position, or a [[[2-(methoxyphenyl)-ethyl]-aminocarbonyl]-methylene]-aminocarbonyl group wherein the group -D-E is bound to the methylene carbon atom, or, if a heteroatom of group A is not bound to the same carbon atom of group B as is group C, C may also represent an oxygen or sulphur atom, an -SO-, -SO_2-, -NH-, -NCH_3-, -N($COCH_3$)-, -N(benzoyl)-, -N(SO_2CH_3)-, -NH-CO-, 1-pyrrolidinylene or 1-piperidinylene group, although generally an oxygen or sulphur atom of group C cannot directly follow an oxygen or sulphur atom or a -CO- group of group A, and an oxygen or sulphenyl or sulphinyl group of group C cannot directly follow a nitrogen atom of group A, and a -CO- group of group C cannot directly follow an oxygen or sulphur atom or a -CO-NH- or -CO-NCH_3- group of group A;

D represents a bond, a straight-chained or branched C_{1-3}-alkylene group or a (C_{1-2}-alkylene)phenylene group; and

E represents a carboxy, sulpho, phosphono, 5-tetrazolyl or O-methyl-phosphono group or a C_{2-5}(alkoxycarbonyl) group wherein the alkoxy moiety may be substituted in the 1- or 2-position by a phenyl group, or E may also represent an aminocarbonyl, methylaminocarbonyl or dimethylaminocarbonyl group;

at least one of the groups A, B, C and D does not

represent a bond, group E cannot directly follow a heteroatom of groups A or C and, if X represents an aminomethyl group, the shortest distance between the amino group and group E is at least 12 bonds;

and the stereoisomers thereof, including the mixtures and salts thereof.

However, most particularly preferred compounds according to the invention include those of formula I wherein

the phenyl ring connected to the group X is unsubstituted and the phenyl ring connected to the group A is substituted by a hydroxy or methoxy group;

X represents an aminomethyl or amidino group in which a hydrogen atom at one of the nitrogen atoms may be replaced by a methoxycarbonyl, ethoxycarbonyl or benzyloxycarbonyl group;

A represents a bond, an oxygen atom, or an -NH-CO-, -CO-NH-, $-CO-NCH_3-$, $-SO_2-NH-$ or $-NH-SO_2-NH-$ group;

B represents a bond, a straight-chained C_{1-5}-alkylene group or a cyclohexylene or phenylene group;

C represents a bond or, if C does not directly follow an oxygen atom or a -CO-NH- or $-CO-NCH_3-$ group of group A, C may also represent a -CO-NH- group, a piperidinylene-N-carbonyl group linked in the 3- or 4-position to group -D-E, a 4-piperazinylene-N-carbonyl or 4-methanylylidene-piperidinocarbonyl group wherein the group -D-E is bound to the methanylylidene group, or C may represent a 4-hydroxy-4-piperidinylene-N-carbonyl, 4-carboxymethyl-4-piperidinylene-N-carbonyl or 4-methoxycarbonylmethylene-piperidinylene-N-carbonyl group

wherein the group -D-E is bound to the 4-position, or C may represent a [[[2-(4-methoxyphenyl)-ethyl]aminocarbonyl]-methylene]-aminocarbonyl group wherein the group -D-E is linked to the methylene carbon atom, or, if C does not directly follow an oxygen atom or a carbonyl group of group A and a heteroatom of group A is not linked to the same carbon atom of B which carries the group C, C may also represent an -NH-CO- group or, if C does not directly follow an oxygen atom of group A and a heteroatom of group A is not linked to the same carbon atom of B which carries group C, C may also represent a 1-piperidinylene group;

D represents a bond or a methylene, ethylene, methylene-phenylene or ethylenephenylene group; and

E represents a carboxyl, methoxycarbonyl, ethoxycarbonyl, benzyloxycarbonyl, aminocarbonyl, dimethylaminocarbonyl or 5-tetrazolyl group;

whilst at least one of the groups A, B, C and D does not represent a bond and E cannot directly follow a heteroatom of groups A or C, and, if X represents an aminomethyl group, the shortest distance between the amino group and group E is at least 12 bonds;

and particularly those compounds of formula I wherein

the biphenylyl group is unsubstituted;

X is an aminomethyl or amidino group in which a hydrogen atom at one of the nitrogen atoms may be replaced by a methoxycarbonyl or benzyloxycarbonyl group;

A represents a bond, an oxygen atom or an -NH-CO- or -CO-NH- group;

B represents a bond, a straight-chained C_{1-5}-alkylene group or a cyclohexylene group;

C represents a bond or, if C does not directly follow a heteroatom or a carbonyl group of group A, C may represent a -CO-NH- group, a piperidinylene-N-carbonyl group linked in the 3- or 4-position to group -D-E, a piperazinylene-N-carbonyl group wherein group -D-E is bound to the 4-position, or a [[[2-(4-methoxyphenyl)-ethyl]-aminocarbonyl]-methylene]-aminocarbonyl group wherein the group -D-E is linked to the methylene carbon atom;

D represents a bond or a methylene or ethylene group; and

E represents a carboxyl, methoxycarbonyl, ethoxycarbonyl or benzyloxycarbonyl group;

whilst at least one of the groups A, B, C and D does not represent a bond and E cannot directly follow a heteroatom of groups A or C, and if X represents an aminomethyl group the shortest distance between the amino group and the group E is at least 12 bonds;

and the stereoisomers, including the mixtures thereof and the salts thereof.

Especially preferred compounds of formula I include:

4-amidino-4'-[(4-carboxymethylpiperidino)carbonyl]-biphenyl;

4-amidino-4'-[(4-carboxymethylpiperazino)carbonyl]-biphenyl;

4-amidino-4'-[(4-carboxycyclohexyl)aminocarbonyl]-biphenyl;

4-amidino-4'-[(4-methoxycarbonylmethylpiperidino)-carbonyl]biphenyl;

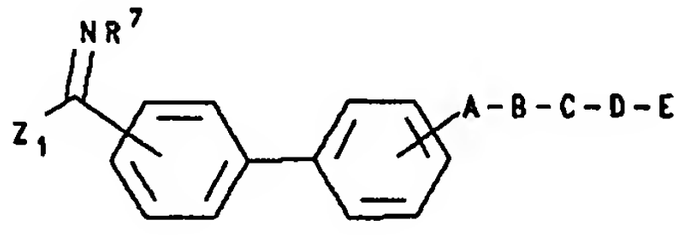
4-amidino-4'-[(4-methoxycarbonylcyclohexyl)-aminocarbonyl]biphenyl; or

4-(N-methoxycarbonylamidino)-4'-[(4-methoxycarbonyl-methylpiperidino)carbonyl]biphenyl;

and the stereoisomers, including the mixtures thereof and the salts thereof.

Viewed from a further aspect the invention also provides a process for preparing the compounds of the invention, said process comprising at least one of the following steps:

a) (to prepare compounds of formula I wherein X contains an amidino group) reacting a compound of formula II



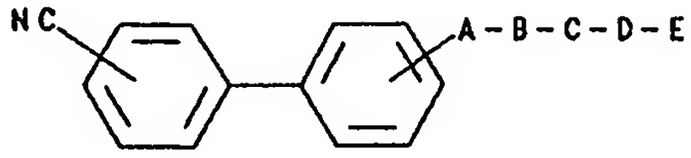
(II)

(wherein A, B, C, D and E are defined as hereinbefore, R_7 represents a hydrogen atom or a C_{1-4}-alkyl group and Z_1 represents an alkoxy or aralkoxy group such as a methoxy, ethoxy, n-propoxy, isopropoxy or benzyloxy group or an alkylthio or aralkylthio group such as a methylthio, ethylthio, n-propylthio or benzylthio group or an amino group) which is optionally formed in the reaction mixture, with an amine of formula III

$NH_2 - R_8$ (III)

(wherein R_8 represents a hydrogen atom, a C_{1-4}-alkyl group, a hydroxy group, a C_{1-3}-alkoxy group or an amino group) or with an acid addition salt thereof;

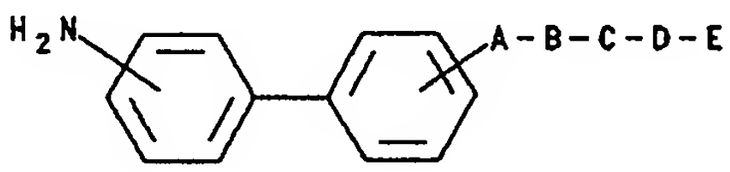
b) (to prepare compounds of formula I wherein X represents an aminomethylene group) reducing a compound of formula IV



(IV)

(wherein A, B, C, D and E are defined as hereinbefore.

c) (to prepare compounds of formula I wherein X represents a guanidino group) reacting a compound of formula V



(V)

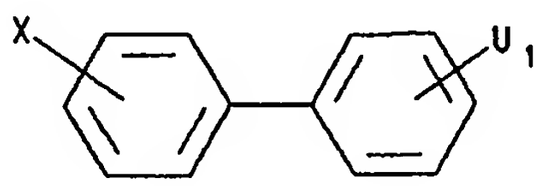
(wherein A, B, C, D and E are defined as hereinbefore) or an acid addition salt thereof, with cyanamide;

d) (to prepare compounds of formula I wherein E represents a carboxyl group) converting a compound of formula VI

(VI)

(wherein A, B, C, D and X are defined as hereinbefore and E', which is bound to a carbon atom, represents a group which can be converted by hydrolysis, treatment with acids, thermolysis or hydrogenolysis into a carboxyl- or bis-(hydroxycarbonyl)methyl group), optionally with subsequent decarboxylation;

e) (to prepare compounds of formula I wherein A represents an $-NR_3-CO-$, $-CO-NR_3-$, $-SO_2-NR_3-$ or $-NR_3-SO_2-$ group) reacting a compound of formula VII



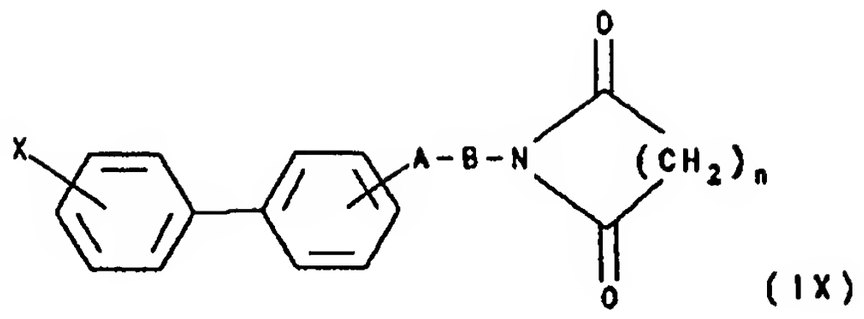
(VII)

with a compound of formula VIII

$$U_2 - C - D - E \qquad \text{(VIII)}$$

(wherein C, D, E and X are defined as hereinbefore, one of the groups U_1 or U_2 represents an HNR_3- group, wherein R_3 is defined as hereinbefore, and the other group U_1 or U_2 represents a $Z_2-A'-$ group, wherein A' represents a carbonyl or sulphonyl group and Z_2 represents a hydroxy group or a nucleophilic leaving group such as a halogen atom, an alkoxy, aralkoxy, aryloxy, alkylthio, arylthio or alkoxycarbonyloxy group, e.g. a chlorine, bromine or iodine atom, a methoxy, ethoxy, benzyloxy, phenoxy, methylthio, phenylthio or isobutyloxy-carbonyloxy group) or with a reactive derivative thereof such as an internal anhydride thereof;

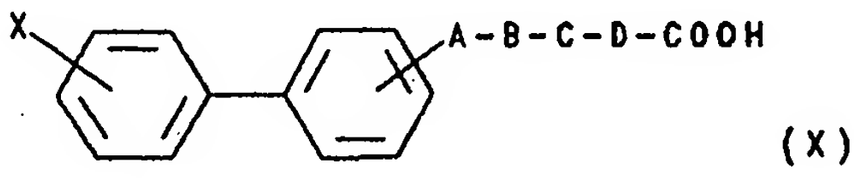
f) (to prepare compounds of formula I wherein the E-D-C group is an $HOOC-(CH_2)_n-CO-NH-$ group) hydrolysing of a compound of formula IX



(IX)

(wherein A, B, X and n are defined as hereinbefore);

g) (to prepare compounds of formula I wherein E represents a C_{2-6}(alkoxycarbonyl) group wherein the alkoxy moiety may be substituted in the 1-, 2- or 3-position by an aryl or pyridyl group or may be substituted in the 2- or 3-position by a pyrrolidino, piperidino, hexamethylene-imino, 2-oxo-1-pyrrolidinyl, morpholino, thiomorpholino or 1,1-dioxido-thiomorpholino group or by a piperazino group optionally substituted in the 4-position by a group R_5) reacting a compound of formula X



(X)

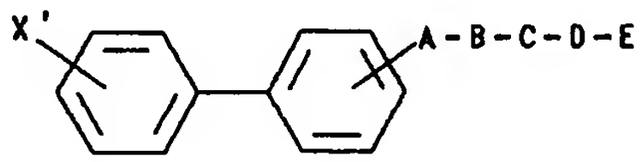
(wherein A, B, C, D and X are defined as hereinbefore) or a reactive derivative thereof, such as an ester, anhydride or halide thereof, with a compound of formula XI

$$H - R_9 \qquad (XI)$$

(wherein R_9 represents a C_{1-5}-alkoxy group wherein the alkoxy moiety may be substituted in the 1-, 2- or 3-position by an aryl or pyridyl group or in the 2- or 3-position by a pyrrolidino, piperidino, hexamethyleneimino, 2-oxo-1-pyrrolidinyl, morpholino,

thiomorpholino or 1,1-dioxido-thiomorpholino group or by a piperazino group optionally substituted in the 4-position by a group R_5);

h) (to prepare compounds of formula I wherein group X contains a cyano, alkoxycarbonyl or aralkoxycarbonyl group) reacting a compound of formula XII



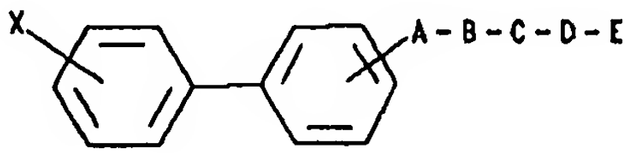
(XII)

(wherein A, B, C, D and E are defined as hereinbefore and X' represents an amino, aminoalkyl, amidino, guanidino or guanidinoalkyl group) with bromocyanogen or with an ester of formula XIII

$$Z_3 - CO - OR_3' \qquad (XIII)$$

(wherein R_3' represents an optionally phenyl-substituted C_{1-3}-alkyl group and
Z_3 represents a nucleophilic leaving group such as a halogen atom, an azido group, an alkoxycarbonyloxy, aralkoxycarbonyloxy or aryloxy group, e.g. a chlorine or bromine atom or a methoxycarbonyloxy, ethoxycarbonyloxy, benzyloxycarbonyloxy or nitrophenyloxy group);

i) (to prepare compounds of formula I wherein A or C represents a sulphinyl or sulphonyl group or R_1 or R_2 represents an alkylsulphinyl or alkylsulphonyl group or E contains a 1-oxidothiomorpholino or 1,1-dioxidothiomorpholino group) oxidising a compound of formula XIV



(XIV)

(wherein A, B, C, D, E and X are defined as hereinbefore with the proviso that A or C represents a sulphur atom or a sulphinyl group or R_1 or R_2 contains a sulphenyl or sulphinyl group or E contains a thiomorpholino or 1-oxidothiomorpholino group);

j) performing any one of steps (a) to (i) above on a compound in which reactive groups are protected by protective groups and subsequently removing the protective groups;

k) separating stereoisomers of a compound of formula I from a mixture thereof; and

l) converting a compound of formula I into a salt thereof or converting a salt of a compound of formula I into the free compound.

The reaction of step (a) is expediently carried out in a solvent such as methanol, ethanol, n-propanol, water, methanol/water, tetrahydrofuran or dioxane at temperatures between 0 and 150°C, preferably at temperatures between 20 and 120°C, with a corresponding free amine or with a corresponding acid addition salt such as ammonium carbonate.

A compound of formula II may be obtained, for example, by reacting a corresponding nitrile with a suitable alcohol such as methanol, ethanol, n-propanol, isopropanol or benzyl alcohol in the presence of an acid such as hydrochloric acid or by reacting a corresponding amide with a trialkyloxonium salt such as triethyloxonium-tetrafluoroborate in a solvent such as methylene chloride, tetrahydrofuran or dioxane at temperatures between 0 and 50°C, but preferably at 20°C, or a corresponding nitrile with hydrogen sulphide, appropriately in a solvent such as pyridine or dimethylformamide and in the presence of a base such as

triethylamine with subsequent alkylation of the resulting thioamide with a suitable alkyl or aralkyl halide.

The reduction of step (b) is preferably carried out in a suitable solvent such as methanol, methanol/water, methanol/water/ammonia, ethanol, ether, tetrahydrofuran, dioxane or dimethylformamide in the presence of catalytically activated hydrogen, e.g. hydrogen in the presence of Raney nickel, platinum or palladium/charcoal, or in the presence of a metal hydride such as sodium borohydride, lithium borohydride or lithium aluminium hydride at temperatures between 0 and 100°C, preferably at temperatures between 20 and 80°C.

The reaction of step (c) is conveniently carried out in a solvent such as dioxane, dioxane/water or tetrahydrofuran, preferably at temperatures between 60 and 120°C, e.g. at the boiling temperature of the reaction mixture.

In the reaction of step (d) examples of convertible functional derivatives of the carboxyl group include unsubstituted or substituted amides, esters, thioesters, trimethylsilylesters, orthoesters, iminoesters, amidines or anhydrides, or a nitrile group which may be converted by hydrolysis into a carboxyl group,
esters with tertiary alcohols, e.g. tert.butylesters, which may be converted by treatment with an acid or thermolysis into a carboxyl group and
esters with aralkanols, e.g. benzylesters, which may be converted by hydrogenolysis into a carboxyl group.

The hydrolysis of step (d) is conveniently carried out either in the presence of an acid such as hydrochloric, sulphuric, phosphoric, trichloroacetic or trifluoroacetic acid, in the presence of a base such as lithium hydroxide, sodium hydroxide or potassium hydroxide in a suitable solvent such as water, water/methanol, ethanol, water/ethanol,

water/isopropanol or water/dioxane at temperatures between -10°C and 120°C, e.g. at temperatures between ambient temperature and the boiling temperature of the reaction mixture. When treating with an organic acid such as trichloroacetic or trifluoroacetic acid, any alcoholic hydroxy groups present may simultaneously be converted into a corresponding acyloxy group such as a trifluoroacetoxy group.

If E' in a compound of formula VI represents a cyano or aminocarbonyl group, these groups may also be converted into a carboxyl group with a nitrite, e.g. sodium nitrite, in the presence of an acid such as sulphuric acid, which may appropriately be used as the solvent at the same time, at temperatures between 0 and 50°C.

If E' in a compound of formula VI represents a tert.butyloxycarbonyl group, for example, the tert.butyl group may also be cleaved by treating with an acid such as trifluoroacetic acid, formic acid, p-toluenesulphonic acid, sulphuric acid, phosphoric acid or polyphosphoric acid, optionally in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran or dioxane, preferably at temperatures between -10°C and 120°C, e.g. at temperatures between 0 and 60°C, or thermally, optionally in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran or dioxane and preferably in the presence of a catalytic amount of an acid such as p-toluenesulphonic acid, sulphuric acid, phosphoric acid or polyphosphoric acid, preferably at the boiling temperature of the solvent used, e.g. at temperatures between 40°C and 100°C.

If E' in a compound of formula VI represents a benzyloxycarbonyl group, for example, the benzyl group may also be hydrogenolytically cleaved in the presence of a hydrogenation catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol,

ethanol/water, glacial acetic acid, ethyl acetate, dioxane or dimethylformamide, preferably at temperatures between 0 and 50°C, e.g. at ambient temperature, under a hydrogen pressure of 1 to 5 bar. During hydrogenolysis, other groups may also be reduced at the same time, e.g. a nitro group may be reduced to an amino group or a benzyloxy group to a hydroxy group.

The subsequent decarboxylation which may be required is preferably carried out in a solvent such as glacial acetic acid at elevated temperatures, e.g. at the boiling temperature of the reaction mixture.

The reaction of step (e) is conveniently carried out in a solvent such as methanol, methylene chloride, chloroform, carbon tetrachloride, ether, tetrahydrofuran, dioxane, benzene, toluene, acetonitrile, dimethylsulphoxide, sulpholane or dimethylformamide, optionally in the presence of an inorganic or organic base, optionally in the presence of a reaction accelerator such as 4-dimethylamino-pyridine, copper or copper(I)chloride or, if Z_2 represents a hydroxy group, optionally in the presence of an acid-activating agent such as N,N'-carbonyldiimidazole or N,N'-dicyclohexylcarbodiimide, optionally in the presence of hydroxybenztriazole or hydroxysuccinimide or optionally in the presence of a dehydrating agent or optionally in the presence of an agent which activates the amino group, at temperatures between -20 and 200°C, but preferably at temperatures between -10 and 160°C.

The hydrolysis of step (f) is conveniently carried out in the presence of a base such as sodium hydroxide or potassium hydroxide in a suitable solvent such as water, water/methanol, ethanol, water/ethanol, water/iso-propanol or water/dioxane at temperatures between -10°C and 120°C, e.g. at temperatures between ambient temperature and the boiling temperature of the reaction mixture.

The reaction of step (g) is conveniently carried

out in a solvent such as tetrahydrofuran, chloroform, dimethylformamide or in a corresponding alcohol in the presence of an acid activating agent or a dehydrating agent, e.g. in the presence of isobutylchloroformate, thionyl chloride, trimethylchlorosilane, hydrochloric acid, sulphuric acid, methanesulphonic acid, p-toluenesulphonic acid, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide or 1-hydroxy-benztriazole, N,N'-carbonyldiimidazole or N,N'-thionyldiimidazole or triphenylphosphine/carbon tetrachloride, or an agent which activates the amino group, e.g. phosphorus trichloride, and optionally in the presence of a base such as sodium carbonate, potassium carbonate, potassium tert.butoxide or 1-hydroxy-benztriazole/triethylamine or in the presence of a tertiary organic base such as triethylamine, N-ethyl-diisopropylamine, N-methyl-morpholine or pyridine, which may simultaneously serve as solvent, at temperatures between -30 and 100°C, but preferably at temperatures between -10 and 80°C. However, the reaction may also be carried out with a corresponding acid halide or acid anhydride optionally in the presence of an acid binding agent as described above.

The reaction of step (h) is conveniently carried out in a solvent such as tetrahydrofuran, chloroform, dimethyl-formamide, dioxane, methylene chloride or diethylether, optionally in the presence of a base such as sodium carbonate, potassium carbonate, potassium tert.butoxide or 1-hydroxy-benzotriazole/triethylamine or in the presence of a tertiary organic base such as triethylamine, N-ethyl-diisopropylamine, N-methyl-morpholine, 4-dimethylaminopyridine or pyridine, which may simultaneously serve as solvent, at temperatures between -30 and 100°C, but preferably at temperatures between -10 and 80°C.

The oxidation of step (i) is preferably carried out

in a solvent or mixture of solvents, e.g. in water, water/pyridine, acetone, glacial acetic acid, methylene chloride, glacial acetic acid/acetanhydride, dilute sulphuric acid or trifluoroacetic acid, at temperatures between -80 and 100°C, depending on the oxidising agent used.

In order to prepare a corresponding S-oxide compound of formula I oxidation is appropriately carried out with one equivalent of the oxidising agent used, e.g. with hydrogen peroxide in glacial acetic acid, trifluoroacetic acid or formic acid at 0 to 20°C or in acetone at 0 to 60°C, with a peracid such as performic acid in glacial acetic acid or trifluoroacetic acid at 0 to 50°C or with m-chloroperbenzoic acid in methylene chloride or chloroform at -20 to 60°C, with sodium metaperiodate in aqueous methanol or ethanol at -15 to 25°C, with bromine in glacial acetic acid or aqueous acetic acid, with N-bromo-succinimide in ethanol, with tert.butyl-hypochlorite in methanol at -80 to -30°C, with iodobenzodichloride in aqueous pyridine at 0 to 50°C, with nitric acid in glacial acetic acid at 0 to 20°C, with chromic acid in glacial acetic acid or in acetone at 0 to 20°C and with sulphurylchloride in methylene chloride at -70°C and the resulting thioether-chlorine complex is conveniently hydrolysed with aqueous ethanol.

In order to prepare an S,S-dioxide compound of formula I, oxidation is expediently carried out with one or with two or more equivalents of the oxidising agent used, e.g. with hydrogen peroxide in glacial acetic acid/acetanhydride, trifluoroacetic acid or in formic acid at 20 to 100°C or in acetone at 0 to 60°C, with a peracid such as performic acid or m-chloroperbenzoic acid in glacial acetic acid, trifluoroacetic acid, methylene chloride or chloroform at temperatures between 0 and 60°C, with nitric acid in glacial acetic acid at 0 to 20°C, with chromic acid or potassium permanganate in

glacial acetic acid, water/sulphuric acid or in acetone at 0 to 20°C.

In reaction steps a) to i) described hereinbefore, any reactive groups present such as hydroxy, carboxy, amino or alkylamino groups may be protected during the reaction by means of conventional protecting groups which are cleaved again after the reaction.

For example, the protective group for a hydroxy group may be a trimethylsilyl, acetyl, benzoyl, tert.butyl, trityl, benzyl or tetrahydropyranyl group, the protecting group for a carboxyl group may be a trimethylsilyl, methyl, ethyl, tert.butyl, benzyl or tetrahydropyranyl group and the protecting group for an amino, alkylamino or imino group may be an acetyl, benzoyl, ethoxycarbonyl, tert.-butoxycarbonyl, benzyloxycarbonyl, benzyl, methoxybenzyl or 2,4-dimethoxybenzyl group and for the amino group a phthalyl group may also be considered.

The optional subsequent cleaving of a protecting group may, for example, be carried out hydrolytically in an aqueous solvent, e.g. in water, isopropanol/water, tetrahydrofuran/water or dioxane/water, in the presence of an acid such as trifluoroacetic acid, hydrochloric or sulphuric acid or in the presence of an alkali metal base such as sodium hydroxide or potassium hydroxide or by ether cleaving, e.g. in the presence of iodotrimethylsilane, at temperatures between 0 and 100°C, preferably at temperatures between 10 and 50°C.

However, a benzyl, methoxybenzyl or benzyloxy-carbonyl group may be cleaved hydrogenolytically, for example, using hydrogen in the presence of a catalyst such as palladium/charcoal in a solvent such as methanol, ethanol, ethyl acetate or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid at temperatures between 0 and 50°C, but preferably at ambient temperature, under a hydrogen pressure of 1 to 7 bar, preferably 3 to 5 bar.

A methoxybenzyl group may also be cleaved in the presence of an oxidising agent such as cerium(IV)-ammonium nitrite in a solvent such as methylene chloride, acetonitrile or acetonitrile/water at temperatures between 0 and 50°C, but preferably at ambient temperature.

However, a 2,4-dimethoxybenzyl group is preferably cleaved in trifluoroacetic acid in the presence of anisole.

A tert.butyl or tert.butyloxycarbonyl group is preferably cleaved by treating with an acid such as trifluoroacetic or hydrochloric acid, optionally using a solvent such as methylene chloride, dioxane or ether.

A phthalyl group is preferably cleaved in the presence of hydrazine or a primary amine such as methylamine, ethylamine or n-butylamine in a solvent such as methanol, ethanol, isopropanol, toluene/water or dioxane at temperatures between 20 and 50°C.

Furthermore, the compounds of formula I obtained may be resolved into their enantiomers and/or diastereomers as mentioned hereinbefore. Thus, for example, cis/trans mixtures may be resolved into their cis and trans isomers, and compounds having at least one optically active carbon atom may be resolved into their enantiomers.

Thus, for example, the cis/trans mixtures obtained may be resolved by chromatography into the cis and trans isomers thereof and the compounds of formula I which occur in racemate form may be separated by methods known per se (see Allinger N. L. and Eliel E. L. in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) into their optical antipodes and compounds of general formula I having at least 2 asymmetric carbon atoms may be separated on the basis of their physical-chemical differences using known methods, e.g. by chromatography and/or fractional crystallisation, into the diastereomers thereof which, if they occur in racemic

form, may subsequently be separated into the enantiomers as mentioned above.

The separation of enantiomers is preferably effected by column separation on chiral phases or by recrystallisation from an optically active solvent or by reacting with an optically active substance which forms salts or derivatives such as esters or amines with the racemic compound, especially acids and the activated derivatives or alcohols thereof, and separation of the diastereomeric salt mixture or derivative thus obtained, e.g. on the basis of their different solubilities, whilst the free antipodes may be released from the pure diastereomeric salts or derivatives by the action of suitable agents. Particularly common, optically active acids include, for example, the D- and L-forms of tartaric and dibenzoyltartaric acid, di-o-tolyl tartaric acid, malic, mandelic, camphorsulphonic, glutamic, aspartic or quinic acid. The optically active alcohol may be (+)- or (-)-menthol, for example, and the optically active acyl group in amides may be, for example, (+)- or (-)-menthyloxycarbonyl.

Moreover, the compounds of formula I obtained may be converted into the salts thereof, particularly for pharmaceutical use the physiologically acceptable salts thereof with inorganic or organic acids. Examples of suitable acids include hydrochloric, hydrobromic, sulphuric, phosphoric, fumaric, succinic, lactic, citric, tartaric or maleic acid.

In addition, the new compounds of formula I thus obtained, if they contain a carboxyl group, may subsequently, if desired, be converted into the addition salts thereof with inorganic or organic bases, more particularly, for pharmaceutical use, into the physiologically acceptable addition salts thereof. Examples of suitable bases include sodium hydroxide, potassium hydroxide, cyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

The compounds of formulae II to XIV used as starting materials are known from the literature in some cases or may be obtained by methods known from the literature (see Examples). Moreover, some of them are described in our as yet unpublished German Patent Application P 40 35 961.1 filed on 2 November 1990.

As already mentioned, the new biphenyl derivatives of formula I and the addition salts thereof, particularly the physiologically acceptable addition salts thereof with inorganic or organic acids or bases, have valuable properties. Thus, the new compounds of formula I wherein X contains an optionally substituted amino, amidino or guanidino group or a group which may optionally be converted in vivo into an optionally substituted amino, amidino or guanidino group, e.g. an amino, amidino or guanidino group substituted by an alkoxycarbonyl group, and -C-D-E contains carboxyl, sulpho, phosphono, O-alkyl-phosphono or 5-tetrazolyl groups or groups which can be converted in vivo into carboxyl, sulpho, phosphono, O-alkyl-phosphono or tetrazolyl groups, e.g. alkoxy-substituted carbonyl groups, have valuable pharmacological properties; in addition to having an inhibitory effect on inflammation and bone degradation, they have, in particular, antithrombotic, antiaggregatory and tumour- or metastasis-inhibiting effects.

The compounds of formula I wherein X represents a cyano group are valuable intermediate products for preparing the corresponding aminomethyl and amidino compounds of formula I.

By way of example, the compounds of formula I were investigated for their biological effects as follows:

Fibrinogen binding to human thrombocytes

The blood obtained by puncturing an antecubital vein is anticoagulated with trisodium citrate (final

concentration: 13 mM) and centrifuged for 10 minutes at 170 xg. The supernatant platelet-rich plasma is poured onto a Sepharose 2B column (Pharmacia) and eluted with a solution of 90 mM common salt, 14 mM trisodium citrate, 5 mM glucose and 50 mM Tris(hydroxymethyl)aminomethane, adjusted to pH 7.4. The gel-filtered platelets (GFP) appearing before the plasma proteins are used for the binding experiments.

50 µl of a 60 mM calcium chloride solution, 50 µl of a 0.6 mM adenosine diphosphate solution, 100 µl of substance solution or solvent and 50 µl of fibrinogen solution (containing 3 µg of ^{125}I fibrinogen) are added to 750 µl of GFP and incubated for 20 minutes at ambient temperature. The non-specific binding is determined in the presence of 3 mg/ml of cold fibrinogen.

900 µl of the incubated material are carefully pipetted onto 250 µl of silicon oil (AP 38: AR 20, 1:2 v/v, Wacker Chemie) in Eppendorf tubes and centrifuged for 2 minutes at 10,000 xg. The aqueous supernatant and some of the oil are drawn off, the tips of the tubes are cut off together with the platelet pellet and the quantity of bound fibrinogen is determined in a gamma counter. The concentration of substance which brings about a 50% inhibition in fibrinogen binding is determined from a series of concentrations and is given as the IC_{50} value.

2. Antithrombotic activity

Method: Thrombocyte aggregation is measured in platelet rich plasma from healthy test subjects using the Born and Cross method (J. Physiol. 170: 397 (1964)). In order to inhibit coagulation the blood is mixed with sodium citrate 3.14% in a ratio by volume of 1:10.

Collagen-induced aggregation: The course of the decrease in optical density of the platelet suspension is

photometrically measured and recorded after the addition of the substance which triggers aggregation. The rate of aggregation is deduced from the gradient angle of the density curve. The point on the curve where there is maximum transmittance is used to calculate the optical density.

The quantity of collagen used is as little as possible but sufficient to give an irreversible reaction curve. Standard commercial collagen produced by Hormonchemie of Munich is used. Before the addition of the collagen the plasma is incubated for 10 minutes at 37°C with the substance.

From the measurements obtained, an EC_{50} is determined graphically, relating to a 50% change in optical density in terms of the inhibition of aggregation.

The Table which follows contains the results found:

Substance (Example No.)	Fibrinogen binding test IC_{50}[nM]	Inhibition of platelet aggregation EC_{50}[nM]
1	290	1,100
1(1)	160	1,100
1(2)	120	7,000
1(3)	1,800	13,000
1(4)	350	1,700
1(5)	65,000	>100,000
1(6)	330	1,200
1(7)	1,900	3,800
1(39)	24	100
1(41)	520	2,600
1(45)	220	2,000
1(47)	470	2,700
1(65)	220	2,400

Substance (Example No.)	Fibrinogen binding test IC_{50}[nM]	Inhibition of platelet aggregation EC_{50}[nM]
1(67)	180	350
1(68)	560	3,400
1(69)	3,100	12,000
1(74)	2,700	10,700
1(80)	31	40
1(94)	-	40
2	210	10,000
2(1)	>10,000	56,000
2(2)	46	45,000
2(11)	360	2,200
3	1,300	16,000
6	570	2,600
6(1)	5,600	3,700
6(2)	14,000	40,000
6(3)	18,000	17,000
6(4)	47,000	4,400
6(8)	5,200	3,400
6(9)	970	1,300
6(46)	19,000	82,000
6(47)	4,900	42,000
6(48)	25,000	590
6(49)	32,000	36,000
6(50)	340	890
6(52)	16,000	38,000
6(56)	5,900	4,900
6(58)	34,000	23,000
6(72)	7,400	3,400
6(74)	24,000	3,200
6(75)	27,000	3,200
6(81)	25,000	34,000
6(86)	5,700	21,000
6(87)	3,800	60

Substance (Example No.)	Fibrinogen binding test IC_{50}[nM]	Inhibition of platelet aggregation EC_{50}[nM]
6(98)	-	370
8(7)	59,000	>10,000
10(1)	800	1,800

Moreover, the compound of Example 8(5) inhibits the collagen-induced thrombocyte aggegation ex vivo in Rhesus monkeys, for example, after oral administration of 1 mg/kg for longer than 8 hours.

The new compounds are well tolerated because after intravenous administration of 60 mg/kg of the compound of Example 1(39), for example, in mice, none of the three animals tested died. Similar results were obtained with the compounds of Example 1, 1(1) and 2(11) at a dosage of 30 mg/kg, whilst during the injection phase with compounds of Examples 1(1) and 2(11) 1 or 2 animals were sedated. Moreover, when 2.0 g/kg of the compound of Example 8(5) was administered by peroral route no toxic effects were observed either in the rat or in the mouse.

In the light of their inhibitory effect on cell-to-cell or cell-to-matrix interactions, the new cyclic imino derivatives of formula I and the physiologically acceptable addition salts thereof are suitable for combating or preventing diseases in which smaller or greater cell aggregates occur or in which cell-to-matrix interactions play a part, e.g. in treating or preventing venous and arterial thrombosis, cerebrovascular diseases, lung embolism, cardiac infarction, arteriosclerosis, osteoporosis and the metastasis of tumours. They are also suitable for parallel therapy in thrombolysis with fibrinolytics or vascular interventions such as transluminal angioplasty or in the

treatment of shock, diabetes and inflammation.

Thus viewed from a further aspect the invention provides a pharmaceutical composition comprising a compound of formula I or a physiologically acceptable salt thereof together with at least one physiologically acceptable carrier or excipient.

Viewed from a still further aspect the invention also provides the use of a compound of formula I or a physiologically acceptable salt thereof for the manufacture of a therapeutic agent for use in combatting conditions in which cell aggregations or cell-matrix interactions occur.

Viewed from a yet still further aspect the invention provides a method of combatting conditions in which cell aggregations or cell-matrix interactions occur which method comprises administering to a human or non-human, preferably mammalian, subject a compound of formula I or a physiologically acceptable salt thereof.

For treating or preventing the diseases mentioned above the dosage is between 0.1 μg and 20 mg/kg body weight, preferably 1 μg to 10 mg/kg body weight, given in up to four doses per day. For this purpose the compounds of formula I produced according to the invention, optionally in conjunction with other active substances, may be incorporated together with one or more inert conventional carriers and/or diluents, e.g. corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene-glycol, propyleneglycol, stearylalcohol, carboxymethyl-cellulose or fatty substances such as hard fat or suitable mixtures thereof, into conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions, solutions, sprays or suppositories.

The invention is illustrated further in a non-limiting fashion by the following Examples in which parts, percentages and ratios are by weight unless otherwise stated other than eluant or solvent ratios which are by volume.

Example I

4'-Cyano-biphenylyl-4-acetic acid

A mixture of 11.3 g of 4'-bromo-biphenylyl-4-acetic acid (melting point: 172-175°C, prepared by reacting 4-acetyl-4'-bromo-biphenyl with morpholine and sulphur and subsequent hydrolysis with potassium hydroxide), 3.48 g of copper(I)-cyanide and 100 ml of dimethylformamide are refluxed for 12 hours, cooled and concentrated by evaporation. The residue is distributed between 1N sodium hydroxide solution and methylene chloride to which a little methanol has been added. The aqueous phase is acidified and extracted with methylene chloride. The methylene chloride phase is treated with activated charcoal, evaporated down, the solid residue is triturated with a mixture of ether and petroleum ether and filtered off.
Yield: 5.1 g (55% of theory),
R_f value: 0.46 (silica gel; methylene chloride/ethanol = 9:1)

The following compound is obtained analogously:

(1) Methyl 4-cyano-biphenylyl-4'-carboxylate
Melting point: 140-142°C.

(The starting methyl 4-bromo-4'-biphenylyl carboxylate (melting point: 140-142°C) is prepared by esterification of 4-bromo-4'-biphenylyl-carboxylic acid with methanolic hydrochloric acid, whereby 4-bromo-4'-biphenylyl-carboxylic acid is prepared by reacting 4-acetyl-4'-bromo-biphenyl with bromine and sodium hydroxide solution).

Example II

4-Cyano-4'-(2-hydroxyethyl)-biphenyl

20.5 g of methyl 4'-cyano-biphenylyl-4-acetate are dissolved in 350 ml of tetrahydrofuran. 1.8 g of lithium borohydride are added with stirring and the mixture is stirred for two days at ambient temperature. The solvent is distilled off, water is added and the precipitate formed is filtered off. It is washed until neutral and used without any further purification.
Yield: 17.2 g (94% of theory)
R_f value: 0.38 (silica gel; methylene chloride)

The following compound is obtained analogously:

(1) 4-Cyano-4'-hydroxymethyl-biphenyl

Example III

4-(2-Bromo-ethyl)-4'-cyano-biphenyl

A mixture of 17.2 g of 4-cyano-4'-(2-hydroxyethyl)-biphenyl, 6.8 ml of pyridine and 75 ml of methylene chloride is cooled to -5°C and 7.8 ml of thionylbromide are added dropwise thereto with stirring. The mixture is allowed to come to ambient temperature, then after 2 hours it is heated to 45°C for one hour and left to stand overnight at ambient temperature. The methylene chloride phase is washed with ice water until the strongly acidic reaction dies away, then filtered and evaporated down. The residue is used without any further purification.
Yield: 20.4 g (93% of theory)
R_f value: 0.60 (silica gel; methylene chloride)

The following compound is obtained analogously:

(1) 4-Bromomethyl-4'-cyano-biphenyl

Example IV

2-[(2-Ethoxycarbonyl-ethyl)-aminosulphonyloxy]-phenol

1.54 g of β-alanine-ethylester-hydrochloride are mixed with 1.9 g of benzo-dioxathiazole-2,2-dioxide, with the addition of 1.55 g of N-ethyl-diisopropylamine dissolved in 10 ml of dimethylformamide, whilst cooling with ice. The mixture is stirred for 2 hours at ambient temperature, the dimethylformamide is eliminated in vacuo (maximum bath temperature 30°C) and the residue is purified by chromatography on silica gel (eluant: cyclohexane/ethyl acetate = 8:2).
Yield: 1.4 g (48% of theory),
R_f value: 0.31 (silica gel; cyclohexane/ethyl acetate = 7:3)

Example V

3-Carboxy-4'-cyano-4-hydroxy-biphenyl

A solution of 12 g of 4-cyano-4'-methoxy-biphenyl in 75 ml of methylene chloride is given to a mixtre of 25 ml of oxalyl chloride, 50 ml of methylene chloride and 25 g of aluminium chloride after stirring for 30 minutes at -20°C. After stirring for 5 hours at -20°C, the reaction mixture is cooled at first with ice and then allowed to come to ambient temperature within 16 hours. After pouring into ice water and stirring for 30 minutes, the reaction mixture is extracted with ethyl acetate and the organic phase is evaporated until the beginning of the crystallisation.
Yield: 10.3 g (75 % of theory)
Melting point: 244- 246°C

Example VI

4-Carboxymethyloxy-4'-cyano-biphenyl

32.9 g of 4-(tert.butyloxycarbonylmethyloxy)-4'-cyano-biphenyl dissolved in 250 ml of methylene chloride is mixed slowly with 137 ml of trifluoroacetic acid. After stirring for 3 hours, the reaction mixture is evaporated to dryness and the solid residue is triturated with water.

Yield: 26.3 g (98 % of theory)

Melting point: 202-204°C

Example VII

4-(tert.Butyloxycarbonylmethyloxy)-4'cyano-biphenyl

Prepared analogously to Example 13 from 4-cyano-4'-hydroxy-biphenyl and tert.butyl bromoacetate.

Melting point: 110-112°C

Example VIII

3-Chlorosulphonyl-4'-cyano-4-methoxy-biphenyl

Prepared by refluxing 6.1 g of sodium 4'-cyano-4-methoxy-3-biphenylyl-sulfonate with 30 ml of phosphorous oxychloride and by subsequent pouring into water.

Yield: 4.7 g (81 % of theory)

R_f value: 0.29 (silica gel; cyclohexane/ethyl acetate = 2:1)

(The starting compound that is used is prepared by reacting 4'-cyano-4-methoxy-biphenyl with chloro sulfonic acid)

Preparation of the final compounds:

Example 1

4-Amidino-4'-[[(2-carboxyethyl)aminocarbonyl]methyl]-biphenyl

---

0.5 g of 4-amidino-4'-[[(2-methoxycarbonylethyl)-aminocarbonyl]methyl]biphenyl are stirred with 10 ml of 1N sodium hydroxide solution for 16 hours at ambient temperature. 0.7 g of ammonium chloride are added, the mixture is evaporated down and the residue is stirred with water. The crystals formed are suction filtered and washed with acetone.

Yield: 0.41 g (97% of theory),

Melting point: above 250°C

R_f value: 0.04 (silica gel; methylene chloride/ethanol/concentrated ammonia = 4:1:0.25)

The following compounds are obtained analogously:

(1) 4-amidino-4'-(4-carboxybutyrylamino)biphenyl

(For saponification a mixture of equal parts of 1N sodium hydroxide solution and methanol is used)

Melting point: above 240°C

R_f value: 0.50 (silica gel; butanol/glacial acetic acid/water = 3:1:1)

(2) 4-amidino-4'-[(3-carboxypropyl)aminocarbonyl]-biphenyl

Melting point: above 260°C

(Lithium hydroxide is used for saponification)

R_f value: 0.06 (silica gel; methylene chloride/ethanol/concentrated ammonia = 4:1:0.25)

(3) 4-amidino-4'-[[(carboxymethylamino)carbonyl]-methoxy]-biphenyl

Melting point: 285°C (decomp.)

Calculated: (x 0.5 H_2O): C 60.71 H 5.39 N 12.49

Found: 60.36 5.27 12.01

(4) 4-amidino-4'-[[(2-carboxyethyl)aminocarbonyl]-methyloxy]biphenyl
Melting point: 290°C (decomp.)
Calculated: (x 0.75 H_2O): C 60.91 H 5.78 N 11.84
Found: 61.38 5.88 11.55

(5) 4-amidino-4'-[[(3-carboxymethylphenyl)-aminocarbonyl]methyl]biphenyl
(Lithium hydroxide is used for saponification)
Melting point: 262-264°C

(6) 4-amidino-4'-[[(4-carboxypiperidino)carbonyl]-methyloxy]biphenyl
Melting point: above 250°C
R_f value: 0.62 (Reversed Phase Ready-made Plate RP8 (E. Merck); methanol/5% sodium chloride solution = 6:4)

(7) 4-amidino-4'-[[(3-carboxypiperidino)carbonyl]-methyloxy]biphenyl
Melting point: above 250°C
R_f value: 0.55 (Reversed Phase Ready-made Plate RP8 (E. Merck); methanol/5% sodium chloride solution = 6:4)

(8) 4-amidino-4'-[N-(4-carboxybutyryl)-N-methylamino]-biphenyl

(9) 4-amidino-4'-[N-(3-carboxypropionyl)-N-methyl-amino]biphenyl

(10) 4-amidino-4'-[(2-carboxyethyl)aminocarbonyl]-biphenyl

(11) 4-aminomethyl-4'-[N-(4-carboxybutyryl)-N-methyl-

amino]biphenyl

(12) 3-(5-carboxyvalerylamino)-3'-guanidinobiphenyl

(13) 4-amidino-4'-[N-[(carboxymethylamino)-carbonylmethyl]-N-methylamino]biphenyl

(14) 4-amidino-3'-bromo-4'-(4-carboxybutyrylamino)-biphenyl

(15) 4-amidino-4'-(4-carboxybutyrylamino)-3',5'-dibromo-biphenyl

(16) 4-amidino-4'-[2-(carboxymethylthio)ethyl]biphenyl

(17) 4-amidino-4'-[(3-carboxypropylthio)methyl]biphenyl

(18) 4-amidino-4'-[(carboxymethyloxy)methyl-carbonylamino]biphenyl

(19) 4-amidino-4'-[(N-carboxymethyl-N-methylamino)-methylcarbonylamino]biphenyl

(20) 4-amidino-4'-[(2-carboxyethylthio)methylcarbonyl]-biphenyl

(21) 4-amidino-4'-(5-carboxypentyloxy)-3'-methoxy-biphenyl

(22) 4-amidino-4'-[[N-(3-carboxy-2-propenyl)-N-methyl-amino]carbonyl]biphenyl

(23) 4-(5-carboxypentyloxy)-4'-(N-methylamidino)-biphenyl

(24) 4-(5-carboxypentyloxy)-4'-(N-methoxyamidino)-biphenyl

(25) 4-(5-carboxypentyloxy)-4'-hydrazidinobiphenyl

(26) 4-[(3-carboxypropyl)aminocarbonyl]-4'-(N-ethoxycarbonylamidino)biphenyl

(27) 4-(N-benzyloxycarbonylamidino)-4'-[(3-carboxy-propyl)aminocarbonyl]biphenyl

(28) 4-amidino-4'-[[[N-(2-carboxyethyl)-N-methylamino]-carbonyl]methyloxy]biphenyl

(29) 4-[2-[N-acetyl-N-(2-carboxyethyl)amino]ethyloxy]-4'-amidinobiphenyl

(30) 4-amidino-4'-[2-[N-(2-carboxyethyl)-N-methane-sulphonylamino]ethyloxy]biphenyl

(31) 4-amidino-4'-[2-[N-benzoyl-N-(2-carboxyethyl)-amino]ethyloxy]biphenyl

(32) 4-amidino-4'-[(3-carboxypropylamino)sulphonyl]-biphenyl

(33) 4-amidino-4'-[[N-(3-carboxypropyl)-N-methylamino]-sulphonyl]biphenyl

(34) 4-amidino-4'-[(2-carboxyethylamino)carbonylamino]-biphenyl

(35) 4-amidino-4'-[N-[[N-(2-carboxyethyl)-N-methyl-amino]carbonyl]-N-methylamino]biphenyl

(36) 4-amidino-4'-[(3-carboxymethylphenyl)-aminocarbonyl]biphenyl
(Lithium hydroxide is used for saponification)
Melting point: above 260°C

(37) 4-amidino-4'-[[3-(2-carboxyethyl)phenyl]-aminocarbonyl]biphenyl
(Lithium hydroxide is used for saponification)
Melting point: above 260°C

(38) 4-amidino-4'-[[3-(2-carboxyethyl)phenyl]-aminocarbonylmethyl]biphenyl
(Lithium hydroxide is used for saponification)
Melting point: 262-264°C

(39) 4-amidino-4'-[(4-carboxymethylpiperidino)-carbonyl]biphenyl hydrochloride
(Lithium hydroxide is used for saponification)
Melting point: 241-245°C (decomp.)

(40) 4-amidino-4'-[(4-carboxymethylpiperidino)methyl]-biphenyl
Melting point: 318-320°C (decomp.)

(41) 4-amidino-4'-[(3-carboxymethylpiperidino)-carbonyl]biphenyl hydrochloride
(Lithium hydroxide is used for saponification)
Melting point: 240-244°C (decomp.)

(42) 4-amidino-4'-[(3-carboxymethylpiperidino)methyl]-biphenyl

(43) 4-amidino-4'-[(3-carboxymethylpyrrolidino)-carbonyl]biphenyl

(44) 4-amidino-4'-[(3-carboxymethylpyrrolidino)-methyl]biphenyl

(45) 4-amidino-4'-[(4-carboxypiperidino)-carbonylmethyl]biphenyl hydrochloride
(Lithium hydroxide is used for saponification)
Melting point: 260-264°C (decomp.)

(46) 4-amidino-4'-[2-(4-carboxypiperidino)ethyl]-biphenyl

(47) 4-amidino-4'-[(3-carboxymethylpiperidino)-carbonylmethyl]biphenyl hydrochloride
(Lithium hydroxide is used for saponification)
R_f value: 0.16 (silica gel; methylene chloride/ethanol = 4:1)

(48) 4-amidino-4'-[2-(3-carboxymethylpiperidino)-ethyl]biphenyl

(49) 4-amidino-4'-[(3-carboxymethylpyrrolidino)-carbonylmethyl]biphenyl

(50) 4-amidino-4'-[2-(3-carboxymethylpyrrolidino)-ethyl]biphenyl

(51) 4-amidino-4'-[(3-carboxypiperidino)-carbonylmethyl]biphenyl

(52) 4-amidino-4'-[2-(3-carboxypiperidino)ethyl]-biphenyl

(53) 4-amidino-4'-(5-carboxypentyloxy)-3'-methane-sulphonylaminobiphenyl

(54) 4-amidino-3'-benzenesulphonylamino-4'-(5-carboxy-pentyloxy)biphenyl

(55) 4-amidino-4'-(4-carboxybutylthio)biphenyl

(56) 4-amidino-4'-[(4-carboxybutyl)sulphinyl]biphenyl

(57) 4-amidino-4'-[(4-carboxybutyl)sulphonyl]biphenyl

(58) 4-amidino-4'-[(3-carboxypropyl)sulphinylmethyl]-

biphenyl

(59) 4-amidino-4'-[(3-carboxypropyl)sulphonylmethyl]-biphenyl

(60) 4-amidino-4'-(5-carboxypentyloxy)-3'-hydroxy-biphenyl

(61) 4-amidino-4'-(5-carboxypentyloxy)-3'-methylthio-biphenyl

(62) 4-amidino-4'-(5-carboxypentyloxy)-3'-methylsulphinylbiphenyl

(63) 4-amidino-4'-(5-carboxypentyloxy)-3'-methyl-sulphonylbiphenyl

(64) 4-amidino-4'-[(4-carboxymethylpiperidino)-carbonylmethyl]biphenyl hydrochloride
(Lithium hydroxide is used for saponification)

(65) 4-amidino-4'-[(4-carboxybutyl)aminocarbonyl]-biphenyl hydrochloride
(Lithium hydroxide is used for saponification)
Melting point: 275-278°C (decomp.)

(66) 4-amidino-4'-(4-carboxybutyloxy)biphenyl
Melting point: above 300°C

Calculated: (x 0.1 H_2O):	C	68.80	H	6.45		N	8.92
Found:		68.80		6.47			8.52

(67) 4-amidino-4'-[(4-carboxymethylpiperazino)-carbonyl]biphenyl hydrochloride
(Lithium hydroxide is used for saponification)
Melting point: above 300°C

Calc. x 1 HCl:	C	59.62	H	5.75	Cl	8.80	N 13.91
Found:		59.09		5.80		9.15	13.30

(68) 4-amidino-4'-[[4-(2-carboxyethyl)piperazino]-carbonyl]biphenyl dihydrochloride
(Lithium hydroxide is used for saponification)
Melting point: 282-286°C (decomp.)

(69) 4-amidino-4'-[(2-carboxyethyl)aminosulphonyl-amino]biphenyl
(Lithium hydroxide is used for saponification)
Melting point: above 265°C
R_f value: 0.84 (Reversed Phase Ready-made Plate RP8 (E. Merck); methanol/10% sodium chloride solution = 60:40)

(70) 4-butylamidino-4'-[(4-carboxymethylpiperidino)-carbonyl]biphenyl

(71) 4-[(4-carboxymethylpiperidino)carbonyl]-4'-methyl-amidinobiphenyl

(72) 4-amidino-4'-[(4-carboxymethylenepiperidino)-carbonyl]biphenyl
Melting point: 317-319°C (decomp.)

(73) 4-amidino-4'-(4-carboxymethyloxyphenyl)biphenyl

(74) 4-amidino-4'-[(4-carboxypiperidino)carbonyl]-biphenyl hydrochloride
(Lithium hydroxide is used for saponification)
Melting point: 303-308°C (decomp.)

(75) 4-aminomethyl-4'-[[(4-carboxypiperidino)carbonyl]-methyl]biphenyl

(76) 4-aminomethyl-4'-[(4-carboxymethylpiperidino)-methyl]biphenyl

(77) 4-amidino-4'-[(4,4-bis-carboxymethylpiperidino)-

carbonyl]biphenyl

(78) 4-aminomethyl-4'-[(4-carboxymethylenepiperidino)-carbonyl]biphenyl

(79) 4-aminomethyl-4'-[(4,4-bis-carboxymethyl-piperidino)carbonyl]biphenyl

(80) 4-amidino-4'-[(4-carboxycyclohexyl)aminocarbonyl]-biphenyl hydrochloride
Melting point: 344-348°C (decomp.)

(81) 4-aminomethyl-3'-[(4-carboxybutyl)aminosulphonyl]-4'-methoxybiphenyl
Melting point: 268-270°C (sinters from 190°C)
R_f value: 0.14 (silica gel; methylene chloride/methanol/concentrated ammonia = 4:1:0.25)

(82) 4-amidino-3'-[(4-carboxybutyl)aminosulphonyl]-4'-methoxybiphenyl
R_f value: 0.13 (silica gel; methylene chloride/methanol/concentrated ammonia = 2:1:0.25)

(83) 4-aminomethyl-3'-[(4-carboxybutyl)aminocarbonyl]-4'-methoxybiphenyl

(84) 4-amidino-3'-[(4-carboxybutyl)aminocarbonyl]-4'-methoxybiphenyl

(85) 4-amidino-4'-(2-carboxyethyloxy)biphenyl

(86) 4-amidino-4'-(carboxymethyloxy)biphenyl

(87) 4-amidino-4'-[(3,3-bis-carboxymethylpropyl)-aminocarbonyl]biphenyl

(88) 4-amidino-4'-[[N-(3,3-bis-carboxymethylpropyl)-N-

methyl]aminocarbonyl]biphenyl

(89) 4-amidino-3'-[(4-carboxycyclohexyl)aminocarbonyl]-4'-methoxybiphenyl
R_f value: 0.40 (silica gel; methylene chloride/methanol = 2:1)

(90) 4-amidino-3'-[(4-carboxycyclohexyl)aminocarbonyl]-4'-hydroxybiphenyl

(91) 4-amidino-3'-[N-(4-carboxycyclohexyl)-N-methyl-aminocarbonyl]-4'-methoxybiphenyl

(92) 4-amidino-3'-[(4-carboxycyclohexyl)-aminosulphonyl]-4'-methoxybiphenyl

(93) 4-aminomethyl-3'-[(4-carboxycyclohexyl)-aminocarbonyl]biphenyl

(94) 4-amidino-4'-[N-(4-carboxycyclohexyl)-N-methyl-aminocarbonyl]biphenyl
Melting point: 323-326°C

(95) 4-amidino-4'-[N-(3-carboxypropyl)-N-methyl-aminocarbonyl]biphenyl
Melting point: 282-285°C (decomp.)

(96) 4-aminomethyl-3'-[N-(4-carboxy-cyclohexyl)-N-methyl-aminocarbonyl]-4'-hydroxy-biphenyl
(Lithium hydroxide is used for saponification)
Melting point: 245-250°C (decomp.)
R_f value: 0.05 (silica gel; methylene chloride/methanol/concentrated ammonia = 2:1:0.5)

(97) 4-aminomethyl-3'-[(4-carboxy-cyclohexyl)-aminocarbonyl]-4'-methoxy-biphenyl

(98) 4-amidino-3'-[N-(4-carboxy-cyclohexyl)-N-methyl-aminocarbonyl]-4'-hydroxy-biphenyl
Melting point: from 290°C (decomp.)
R_f value: 0.34 (silica gel; methylene chloride/methanol = 2:1)

Example 2

4-Amidino-4'-(5-carboxypentyloxy)biphenyl hydrochloride

0.5 g of di[4-amidino-4'-(5-methoxycarbonyl-pentyloxy)biphenyl] dihydrogencarbonate are stirred in 15 ml of 8N hydrochloric acid for 5 weeks at ambient temperature and 5 days at 40°C. The mixture is diluted with water, filtered and the residue is washed with water and acetone.
Yield: 0.43 g (92% of theory),
Melting point: above 250°C
Calculated (x 0.6 HCl): C 65.53 H 6.54 N 8.04 Cl 6.11
Found: 65.30 6.51 7.55 6.31

The following compounds are obtained analogously:

(1) 4-amidino-4'-(3-carboxypropyloxy)biphenyl
Melting point: above 290°C
Calculated (x 0.75 HCl x 0.25 H_2O):
C 61.84 H 5.88 N 8.48 Cl 8.05
Found: 61.85 5.90 8.46 8.27

(2) 4-amidino-4'-(4-carboxybutyloxy)biphenyl

(3) 4-amidino-4'-(5-carboxypentyloxy)-3'-nitrobiphenyl

(4) 4-amidino-3'-amino-4'-(5-carboxypentyloxy)biphenyl

(5) 3-acetylamino-4'-amidino-4-(5-carboxypentyloxy)-biphenyl

(6) 4-amidino-3'-benzoylamino-4'-(5-carboxypentyloxy)-biphenyl

(7) 4-amidino-4'-(5-carboxypentyloxy)-3-chlorobiphenyl

(8) 4-amidino-4'-(5-carboxypentyloxy)-3-fluorobiphenyl

(9) 4-amidino-4'-(5-carboxypentyloxy)-2',3'-dimethyl-biphenyl

(10) 4-amidino-4'-(5-carboxypentyloxy)-3'-trifluoromethylbiphenyl

(11) 4-amidino-4'-[[2-carboxy-1-[[2-(4-methoxyphenyl)-ethyl]aminocarbonyl]ethylamino]carbonylmethyl]biphenyl hydrochloride
(One works in a 1:1 mixture of 2N hydrochloric acid and tetrahydrofuran; reaction lasts 72 hours)
R_f value: 0.50 (Reversed Phase Ready-made Plate RP18 (E. Merck); acetonitrile/water/acetic acid = 5:5:0.1)

Example 3

4-Amidino-4'-[[[2-carboxy-1-[[2-(4-methoxyphenyl)-ethyl]aminocarbonyl]ethylamino]carbonylmethyl]-aminocarbonyl]biphenyl hydrochloride

---

0.67 g of 4-(N-benzyloxycarbonylamidino)-4'-[[[2-benzyloxycarbonyl-1-[[2-(4-methoxyphenyl)ethyl]-aminocarbonyl]ethylamino]carbonylmethyl]aminocarbonyl]-biphenyl are hydrogenated in 100 ml of methanol with hydrogen under 5 bars of pressure in the presence of 0.2 g of 5% palladium charcoal at ambient temperature for 2 hours. The catalyst is filtered off, the filtrate is washed with methanol and a little 1N hydrochloric acid and evaporated down. The residue is triturated with ether and filtered off.

Yield: 0.48 g (92% of theory),
Melting point: 202-205°C (decomp.)

The following compounds are obtained analogously:

(1) 4-[(3-carboxypropylamino)carbonyl]-4'-(N-methoxycarbonylamidino)biphenyl
(Dimethylformamide is used as solvent and 10% palladium/charcoal as catalyst)

(2) 4-amidino-4'-[(4-carboxymethyl-4-hydroxy-piperidino)carbonyl]biphenyl

(3) 4-[(4-carboxymethylpiperidino)carbonyl]-4'-(N-methoxycarbonylamidino)biphenyl
One works using 10% palladium/charcoal in dioxane
Melting point: 194-196°C (decomp.)
R_f value: 0.14 (silica gel; methylene chloride/ethanol = 9:1)

Example 4

4-Amidino-4'-[2-[(2-carboxyethyl)carbonylamino]ethyl]-biphenyl

---

0.27 g of 4-amidino-4'-(2-succinimidoethyl)-biphenyl are dissolved in 10 ml of dimethylsulphoxide, mixed with 0.8 ml of 1N sodium hydroxide solution and stirred for 5 hours at ambient temperature. The precipitate formed is filtered off, washed with dimethylsulphoxide, digested with 0.01N hydrochloric acid, suction filtered and washed with water.
Yield: 0.07 g (25% of theory),
Melting point: above 240°C
R_f value: 0.51 (silica gel; methylene chloride/methanol = 8:2)

Example 5

4-Amidino-4'-[(4-benzyloxycarbonylmethylpiperidino)-carbonyl]biphenyl toluenesulphonate

---

A mixture of 1.6 g of 4-amidino-4'-[(4-carbonyl-methylpiperidino)carbonyl]biphenyl hydrochloride, 50 ml of benzyl alcohol and 1 g of p-toluenesulphonic acid is heated to 70°C with stirring for 4 hours under 100 mbar and then evaporated down in a water jet vacuum at 140-150°C. The residue was triturated with ether, the solid product obtained was filtered off and dissolved in dimethylformamide, the solution was evaporated down and the residue was triturated with ether.
Yield: 2.46 g (98% of theory),
Melting point: 218-223°C (decomp.)

The following compounds were obtained analogously, in each case working in dimethylformamide with a 12-fold molar excess of the alcohol in question and a 15-fold excess of p-toluenesulphonic acid:

(1) 4-amidino-4'[[4-(n-butyloxycarbonylmethyl)-piperidino]carbonyl]biphenyl toluenesulphonate

(2) 4-amidino-4'-[[4-(2-phenylethyl)oxycarbonylmethyl-piperidino]carbonyl]biphenyl toluenesulphonate

(3) 4-amidino-4'-[[4-[2-(2-oxo-pyrrolidinyl)ethyl]-oxycarbonylmethylpiperidino]carbonyl]biphenyl toluenesulphonate

(4) 4-amidino-4'-[[4-[(3-pyridyl)methyl]oxycarbonyl-methylpiperidino]carbonyl]biphenyl toluenesulphonate

(5) 4-amidino-4'-[[4-(2-morpholinoethyl)oxycarbonyl-methylpiperidino]carbonyl]biphenyl toluenesulphonate

(6) 4-amidino-4'-[[4-(2-thiomorpholinoethyl)-oxycarbonylmethylpiperidino]carbonyl]biphenyl

(7) 4-[[4-(n-butyloxycarbonylmethyl)piperidino]-carbonyl]-4'-(N-methylamidino)biphenyl

Example 6

Di-[4-Amidino-4'-(5-methoxycarbonylpentyloxy)biphenyl] dihydrogencarbonate

---

75 ml of methanol are covered with 30 ml of petroleum ether and hydrogen chloride gas is introduced, whilst cooling with ice, until saturation point. Then 2.1 g of 4-cyano-4'-(5-ethoxycarbonylpentyloxy)biphenyl are added and the mixture is stirred for 18 hours at ambient temperature. It is evaporated to dryness in vacuo, the residue is suspended in methanol, 5.36 g of ammonium carbonate are added and the mixture is stirred for 16 hours at ambient temperature. The precipitate obtained is filtered off and purified by stirring with methylene chloride/methanol (85:15) and water.
Yield: 1.75 g (75% of theory),
Melting point: 185-189°C (decomp.)

Calculated (x 0.5 H_2CO_3):	C	66.31	H	6.74	N 7.55
Found:		66.75		6.85	7.41

The following compounds are obtained analogously:

(1) 4-amidino-4'-(4-methoxycarbonylbutyrylamino)-biphenyl hydrochloride
Melting point: from 210°C (decomp.)
R_f value: 0.13 (silica gel; ethyl acetate/ethanol = 7:3)

(2) 4-amidino-4'-[[(4-methoxycarbonylmethyl)-aminocarbonyl]methyloxy]biphenyl hydrochloride
Melting point: 223-225°C (decomp.)
R_f value: 0.06 (silica gel; methylene chloride/methanol

= 10:1)

(3) 4-amidino-4'-[[(2-methoxycarbonylethyl)-aminocarbonyl]methyloxy]biphenyl hydrochloride
Melting point: 155°C (decomp.)
R_f value: 0.18 (silica gel; methylene chloride/methanol = 10:1)

(4) 4-amidino-4'-[[3-(methoxycarbonylmethyl)phenyl]-aminocarbonyl]biphenyl hydrochloride
Melting point: over 260°C
R_f value: 0.27 (silica gel; methylene chloride/ethanol = 4:1)

(5) 4-amidino-4'-[(2-methoxycarbonylethyl)-aminocarbonylmethyl]biphenyl
[The product is purified by chromatography on silica gel (eluant: methylene chloride/ethanol/concentrated ammonia = 4:1:0.25)]
R_f value: 0.20 (silica gel; methylene chloride/ethanol/concentrated ammonia = 4:1:0.25)

(6) 4-amidino-4'-[(3-methoxycarbonylpropyl)-aminocarbonyl]biphenyl hydrochloride
Melting point: 210-212°C
R_f value: 0.17 (silica gel; methylene chloride/ethanol/concentrated ammonia = 4:1:0.25)

(7) 4-amidino-4'-[N-(3-methoxycarbonylbutyryl)-N-methylamino]biphenyl hydrochloride

(8) 4-amidino-4'-(3-methoxycarbonylpropyloxy)biphenyl dihydrogencarbonate
Melting point: 203-205°C

(9) 4-amidino-4'-(4-methoxycarbonylbutyloxy)biphenyl hydrochloride

(A 10:1 mixture of methanol and concentrated aqueous ammonia is used to convert the iminoester obtained as an intermediate product into the amidine)
Melting point: 190-194°C

(10) 4-amidino-4'-[N-(3-methoxycarbonylpropionyl)-N-methylamino]biphenyl hydrochloride

(11) 4-amidino-4'-[(2-methoxycarbonylethyl)-aminocarbonyl]biphenyl hydrochloride

(12) 4-amidino-4'-[N-[(methoxycarbonylmethyl)-aminocarbonylmethyl]-N-methylamino]biphenyl hydrochloride

(13) 4-amidino-3'-bromo-4'-[(4-methoxycarbonylbutyryl)-amino]biphenyl hydrochloride

(14) 4-amidino-3',5'-dibromo-4'-[(4-methoxycarbonyl-butyryl)amino]biphenyl hydrochloride

(15) 4-amidino-4'-(5-methoxycarbonylpentyloxy)-3'-nitro-biphenyl hydrochloride

(16) 4-amidino-3'-amino-4'-(5-methoxycarbonyl-pentyloxy)biphenyl hydrochloride

(17) 3-acetylamino-4'-amidino-4-(5-methoxycarbonyl-pentyloxy)biphenyl hydrochloride

(18) 4-amidino-3'-benzoylamino-4'-(5-methoxycarbonyl-pentyloxy)biphenyl hydrochloride

(19) 4-amidino-3'-methanesulphonylamino-4'-(5-methoxycarbonylpentyloxy)biphenyl hydrochloride

(20) 4-amidino-3'-benzenesulphonylamino-4'-[(5-

methoxycarbonylpentyloxy)biphenyl hydrochloride

(21) 4-amidino-4'-(4-methoxycarbonylbutylthio)biphenyl hydrochloride

(22) 4-amidino-4'-[(4-methoxycarbonylbutyl)sulphonyl]-biphenyl hydrochloride

(23) 4-amidino-4'-[2-(methoxycarbonylmethylthio)-ethyl]biphenyl hydrochloride

(24) 4-amidino-4'-[(3-methoxycarbonylpropylthio)-methyl]biphenyl hydrochloride

(25) 4-amidino-4'-[(3-methoxycarbonylpropyl)-sulphonylmethyl]biphenyl hydrochloride

(26) 4-amidino-4'-[[(methoxycarbonylmethyloxy)methyl]-carbonylamino]biphenyl hydrochloride

(27) 4-amidino-4'-[[N-(methoxycarbonylmethyl)-N-methyl-amino]methyl]carbonylamino]biphenyl hydrochloride

(28) 4-amidino-4'-[(2-methoxycarbonylethylthio)methyl-carbonyl]biphenyl hydrochloride

(29) 4-amidino-3'-hydroxy-4'-(5-methoxycarbonyl-pentyloxy)biphenyl hydrochloride

(30) 4-amidino-3'-methoxy-4'-(5-methoxycarbonyl-pentyloxy]biphenyl hydrochloride

(31) 4-amidino-3-chloro-4'-(5-methoxycarbonyl-pentyloxy)biphenyl hydrochloride

(32) 4-amidino-3-fluoro-4'-(5-methoxycarbonyl-pentyloxy)biphenyl hydrochloride

(33) 4-amidino-2',3'-dimethyl-4'-(5-methoxycarbonyl-pentyloxy)biphenyl hydrochloride

(34) 4-amidino-4'-(5-methoxycarbonyl-pentyloxy)-3'-trifluoromethylbiphenyl hydrochloride

(35) 4-amidino-4'-[[N-(3-methoxycarbonyl-2-propenyl)-N-methylamino]carbonyl]biphenyl hydrochloride

(36) 4-[(5-methoxycarbonylpentyloxy)-4'-(N-methyl-amidino)biphenyl
(The iminoester is taken up in absolute methanol and reacted with a 20-fold excess of a methanolic methylamine solution)

(37) 4-amidino-4'-[[[N-(2-methoxycarbonylethyl)-N-methylamino]carbonyl]methyloxy]biphenyl hydrochloride

(38) 4-[2-[N-acetyl-N-(2-methoxycarbonylethyl)amino]-ethyloxy]-4'-amidinobiphenyl hydrochloride

(39) 4-amidino-4'-[2-[N-methanesulphonyl-N-(2-methoxycarbonylethyl)amino]ethyloxy]biphenyl hydrochloride

(40) 4-amidino-4'-[2-[N-benzoyl-N-(2-methoxycarbonyl-ethyl)amino]ethyloxy]biphenyl hydrochloride

(41) 4-amidino-4'-[(3-methoxycarbonylpropylamino)-sulphonyl]biphenyl hydrochloride

(42) 4-amidino-4'-[[N-(3-methoxycarbonylpropyl)-N-methylamino]sulphonyl]biphenyl hydrochloride

(43) 4-amidino-4'-[(2-methoxycarbonylethyl)-aminocarbonylamino]biphenyl hydrochloride

(44) 4-amidino-4'-[N-[[N-(2-methoxycarbonylethyl)-N-methylamino]carbonyl]-N-methylamino]biphenyl hydrochloride

(45) 4-amidino-4'-[[3-(2-methoxycarbonylethyl)phenyl]-aminocarbonyl]biphenyl hydrochloride
Melting point: 266-268°C (decomp.)

(46) 4-amidino-4'-[[[3-(methoxycarbonylmethyl)phenyl]-aminocarbonyl]methyl]biphenyl hydrochloride
R_f value: 0.48 (silica gel; methylene chloride/ethanol = 4:1)

(47) 4-amidino-4'-[[[3-(2-methoxycarbonylethyl)phenyl]-aminocarbonyl]methyl]biphenyl hydrochloride
R_f value: 0.38 (silica gel; methylene chloride/ethanol = 4:1)

(48) 4-amidino-4'-[[(4-methoxycarbonylpiperidino)-carbonyl]methyloxy]biphenyl hydrochloride
Melting point: 240°C (decomp.)
R_f value: 0.33 (silica gel; methylene chloride/ethanol = 9:1)

(49) 4-amidino-4'-[[(3-methoxycarbonylpiperidino)-carbonyl]methyloxy]biphenyl hydrochloride
R_f value: 0.78 (silica gel; methylene chloride/ethanol = 8:2)

(50) 4-amidino-4'-[(4-methoxycarbonylmethylpiperidino)-carbonyl]biphenyl hydrochloride
Melting point: 268-270°C

(51) 4-amidino-4'-[(4-methoxycarbonylmethylpiperidino)-methyl]biphenyl hydrochloride
Melting point: 148-150°C (decomp.)

(52) 4-amidino-4'-[(3-methoxycarbonylmethylpiperidino)-carbonyl]biphenyl hydrochloride
Melting point: 277-280°C

(53) 4-amidino-4'-[(3-methoxycarbonylmethylpiperidino)-methyl]biphenyl hydrochloride

(54) 4-amidino-4'-[(3-methoxycarbonylmethyl-pyrrolidino)carbonyl]biphenyl hydrochloride

(55) 4-amidino-4'-[(3-methoxycarbonylmethyl-pyrrolidino)methyl]biphenyl hydrochloride

(56) 4-amidino-4'-[(4-methoxycarbonylpiperidino)-carbonylmethyl]biphenyl hydrochloride
Melting point: 224-228°C (decomp.)

(57) 4-amidino-4'-[2-(4-methoxycarbonylpiperidino)-ethyl]biphenyl hydrochloride

(58) 4-amidino-4'-[(3-methoxycarbonylmethylpiperidino)-carbonylmethyl]biphenyl hydrochloride
Melting point: 166-172°C

(59) 4-amidino-4'-[2-(3-methoxycarbonylmethyl-piperidino)ethyl]biphenyl hydrochloride

(60) 4-amidino-4'-[(3-methoxycarbonylmethyl-pyrrolidino)carbonylmethyl]biphenyl hydrochloride

(61) 4-amidino-4'-[2-(3-methoxycarbonylmethyl-pyrrolidino)ethyl]biphenyl hydrochloride

(62) 4-amidino-4'-[(3-methoxycarbonylpiperidino)-carbonylmethyl]biphenyl hydrochloride

(63) 4-amidino-4'-[2-(3-methoxycarbonylpiperidino)-

ethyl]biphenyl hydrochloride

(64) 4-amidino-4-(4-sulphobutyloxy)biphenyl

(65) 4-amidino-4'-(4-phosphonobutyloxy)biphenyl hydrochloride

(66) 4-amidino-4'-[4-(O-methyl-phosphono)butyloxy]-biphenyl hydrochloride

(67) 4-amidino-4'-(5-methoxycarbonylpentyloxy)-3'-methylthiobiphenyl hydrochloride

(68) 4-amidino-4'-(5-methoxycarbonylpentyloxy)-3'-methylsulphonylbiphenyl hydrochloride

(69) 4-amidino-4'-[3-(5-tetrazolyl)propyloxy]biphenyl hydrochloride

(70) 4-amidino-4'-[[2-methoxycarbonyl-1-[[2-(4-methoxy-phenyl)ethyl]aminocarbonyl]ethylamino]carbonylmethyl]-biphenyl
R_f value: 0.11 (silica gel; methylene chloride/methanol = 9:1)

(71) 4-amidino-4'-[(4-methoxycarbonylmethylpiperidino)-carbonylmethyl]biphenyl hydrochloride
Melting point: 172-177°C

(72) 4-amidino-4'-[(4-methoxycarbonylbutyl)amino-carbonyl]biphenyl hydrochloride
Melting point: 208-212°C

(73) 4-amidino-4'-[(4-ethoxycarbonylmethylpiperidino)-carbonyl]biphenyl
R_f value: 0.19 (silica gel; methylene chloride/ethanol = 4:1)

(74) 4-amidino-4'-[(4-methoxycarbonylmethylpiperazino)-carbonyl]biphenyl dihydrochloride
Melting point: 274-276°C

(75) 4-amidino-4'-[[(4-(2-methoxycarbonylethyl)-piperazino]carbonyl]biphenyl dihydrochloride
Melting point: 292-296°C (decomp.)
Calculated (x 2 HCl x H_2O): C 54.53 H 6.23 N 11.54 Cl 14.61
Found: 54.44 5.93 11.50 14.41

(76) 4-amidino-4'-[(2-methoxycarbonylethyl)-aminosulphonylamino]biphenyl hydrochloride
Melting point: sinters above 176°C (decomp.)
Calculated: C 48.63 H 5.32 N 12.97 S 7.42 Cl 9.03
Found: 48.58 5.27 12.66 7.51 8.81

(77) 4-(n-butyl-amidino)-4'-[(4-methoxycarbonylmethyl-piperidino)carbonyl]biphenyl
(n-butylamine is used in the second stage of the reaction).

(78) 4-[(4-methoxycarbonylmethylpiperidino)carbonyl]-4'-(N-methylamidino)biphenyl
(Aqueous methylamine solution is used in the second stage of the reaction).

(79) 4-amidino-4'-[(4-methoxycarbonylmethylene-piperidino)carbonyl]biphenyl
Melting point: 298-300°C (decomp.)

(80) 4-amidino-4'-(4-methoxycarbonylmethyloxyphenyl)-biphenyl

(81) 4-amidino-4'-[(4-methoxycarbonylpiperidino)-carbonyl]biphenyl
Melting point: 294-296°C (decomp.)

(82) 4-amidino-4'-[(4-dimethylaminocarbonylmethyl-piperidino)carbonyl]biphenyl

(83) 4-amidino-4'-[(4-sulphomethylpiperidino)carbonyl]-biphenyl
Melting point:

(84) 4-amidino-4'-[(4-(5-tetrazolylmethyl)piperidino]-carbonyl]biphenyl

(85) 4-amidino-4'-[(4,4-bis-methoxycarbonylmethyl-piperidino)carbonyl]biphenyl

(86) 4-amidino-4'-(aminocarbonylmethylaminocarbonyl)-biphenyl hydrochloride
Prepared from 4-cyano-4'-(methoxycarbonylmethyl-aminocarbonyl)biphenyl
Melting point: above 260°C
R_f value: 0.28 (silica gel; methylene chloride/ethanol = 4:1)

(87) 4-amidino-4'-[(4-methoxycarbonylcyclohexyl)-aminocarbonyl]biphenyl hydrochloride
Melting point: 302-305°C (decomp.)

(88) 4-amidino-4'-(2-methoxycarbonylethyloxy)biphenyl

(89) 4-amidino-4'-(methoxycarbonylmethyloxy)biphenyl

(90) 4-amidino-4'-[(3,3-bis-methoxycarbonylmethyl-propyl)aminocarbonyl]biphenyl

(91) 4-amidino-4'-[N-(3,3-bis-methoxycarbonylmethyl-propyl)-N-methylaminocarbonyl]biphenyl

(92) 4-amidino-4'-methoxy-3'-[(4-methoxycarbonylbutyl)-aminosulphonyl]biphenyl hydrochloride

R_f value: 0.19 (silica gel; methylene chloride/methanol/concentrated ammonia = 4:1:0.25)

(93) 4-amidino-4'-methoxy-3'-[(4-methoxycarbonylbutyl)-aminocarbonyl]biphenyl

(94) 4-amidino-4'-methoxy-3'-[(4-methoxycarbonyl-cyclohexyl)aminocarbonyl]biphenyl
R_f value: 0.15 (silica gel; methylene chloride/methanol = 9:1)

(95) 4-amidino-4'-hydroxy-3'-[(4-methoxycarbonyl-cyclohexyl)aminocarbonyl]biphenyl

(96) 4-amidino-4'-methoxy-3'-[N-(4-methoxycarbonyl-cyclohexyl)-N-methylaminocarbonyl]biphenyl

(97) 4-amidino-4'-methoxy-3'-[(4-methoxycarbonyl-cyclohexyl)aminosulphonyl]biphenyl

(98) 4-amidino-4'-[N-(4-methoxycarbonylcyclohexyl)-N-methylaminocarbonyl]biphenyl hydrochloride
Melting point: 295-300°C

(99) 4-amidino-4'-[N-(3-methoxycarbonylpropyl)-N-methylaminocarbonyl]biphenyl
Melting point: 235-238°C (decomp.)

(100) 4-amidino-4'-hydroxy-3'-[N-(4-methoxycarbonyl-cyclohexyl)-N-methyl-aminocarbonyl]-biphenyl
Melting point: from 195°C (decomp.)
R_f value: 0.12 (silica gel; methylene chloride/methanol = 9:1)

Example 7

4-Hydrazidino-4'-(5-methoxycarbonylpentyloxy)biphenyl

4-Amidino-4'-(5-methoxycarbonylpentyloxy)biphenyl hydrochloride is reacted with a 30-fold excess of hydrazine in methanol at ambient temperature. The reaction lasts for 3 days.

The following compound is obtained analogously:

(1) 4-(N-methoxy-amidino)-4'-(5-methoxycarbonyl-pentyloxy)biphenyl
(O-methyl-hydroxylamine hydrochloride and ethyl-diisopropylamine are used as base)

Example 8

4-(N-Ethoxycarbonylamidino)-4'-[(4-methoxycarbonyl-methylpiperidino)carbonyl]biphenyl

---

0.4 g of 4-amidino-4'-[(4-methoxycarbonylmethyl-piperidino)carbonyl]biphenyl hydrochloride and 0.11 ml of ethyl chloroformate in 80 ml of methylene chloride are mixed with 0.1N sodium hydroxide solution, with vigorous stirring, until the pH of the mixture is maintained at 9. The organic phase is separated off and evaporated to dryness.
Yield: 0.27 g (60% of theory),
R_f value: 0.60 (silica gel; methylene chloride/ethanol = 9:1)

The following compounds are obtained analogously:

(1) 4-(N-methoxycarbonylamidino)-4'-[(3-methoxycarbonylpropylamino)carbonyl]biphenyl

(2) 4-[(3-benzyloxycarbonylpropyl)aminocarbonyl]-4'-(N-

methoxycarbonylamidino)biphenyl

(3) 4-(N-benzyloxycarbonylamidino)-4'-[(3-methoxycarbonylpropyl)aminocarbonyl]biphenyl

(4) 4-(N-ethoxycarbonylamidino)-4'-[(3-methoxycarbonyl-propyl)aminocabonyl]biphenyl

(5) 4-(N-methoxycarbonylamidino)-4'-[(4-methoxycarbonylmethylpiperidino)carbonyl]biphenyl
R_f value: 0.59 (silica gel; methylene chloride/ethanol = 9:1)

(6) 4-(N-benzyloxycarbonylamidino)-4'-[(4-methoxy-carbonylmethylpiperidino)carbonyl]biphenyl
Melting point: 139-142°C
R_f value: 0.66 (silica gel; methylene chloride/methanol = 9:1)

(7) 4-(N-ethoxycarbonylamidino)-4'-[(4-ethoxycarbonyl-methylpiperidino)carbonyl]biphenyl
Melting point: 126-130°C
R_f value: 0.57 (silica gel; methylene chloride/ethanol = 9:1)

(8) 4-(N-benzyloxycarbonylmethylpiperidino)carbonyl]-4'-(N-methoxycarbonylamidino)biphenyl
Melting point: 126-128°C
R_f value: 0.63 (silica gel; cyclohexane/ethyl acetate = 1:3)

(9) 4-(N-methoxycarbonylamidino)-4'-[(4-methoxycarbonyl-cyclohexyl)aminocarbonyl]biphenyl
Melting point: 349-351°C (decomp.)

(10) 4-(N-methoxycarbonyl-amidino)-4'-[N-(4-methoxycarbonyl-cyclohexyl)-N-methyl-aminocarbonyl]-

biphenyl
Melting point: 218-220°C

Example 9

4-Amidino-4'-[(4-methoxycarbonylbutyl)sulphinyl]-biphenyl

Prepared from 4-amidino-4'-(4-methoxycarbonyl-butylthio)biphenyl by oxidation with m-chloro-perbenzoic acid in methylene chloride at -20°C for 15 hours.

The following compounds are obtained analogously:

(1) 4-amidino-4'-[[4-[[2-(1-oxido-thiomorpholino)-ethyl]oxycarbonylmethyl]piperidino]carbonyl]biphenyl

(2) 4-amidino-4'-[(3-methoxycarbonylpropyl)sulphinyl-methyl]biphenyl

(3) 4-amidino-4'-(5-methoxycarbonylpentyloxy)-3'-methylsulphinylbiphenyl

Example 10

4-Aminomethyl-4'-[(4-methoxycarbonylmethylpiperidino)-carbonyl]biphenyl hydrochloride

---

1.89 g of 4-cyano-4'-[(4-methoxycarbonylmethyl-piperidino)carbonyl]biphenyl are dissolved in 40 ml of methanol to which 2 ml of methanolic hydrochloric acid have been added. Hydrogenation is carried out with hydrogen under 5 bars of pressure at ambient temperature in the presence of 0.4 g of 10% palladium/charcoal. After 2.2 hours the catalyst is filtered off and the filtrate is evaporated down. The residue is purified by chromatography on silica gel (eluant: methylene chloride/methanol = 9:1)

Yield: 0.78 g (37% of theory),
Melting point: 188-192°C
R_f value: 0.57 (silica gel; methylene chloride/methanol = 4:1)

The following compounds are obtained analogously:

(1) 4-aminomethyl-4'-[(4-carboxymethylpiperidino)-carbonyl]biphenyl hydrochloride
The compound is formed as a by-product in the mixture described above in a 15% yield.
Melting point: 160-164°C
R_f value: 0.16 (silica gel; methylene chloride/methanol = 4:1)

(2) 4-aminomethyl-4'-[[(4-methoxycarbonylpiperidino)-carbonyl]methyl]biphenyl

(3) 4-aminomethyl-4'-[(4-methoxycarbonylmethyl-piperidino)methyl]biphenyl

(4) 4-aminomethyl-4'-[(4,4-bis-methoxycarbonylmethyl-piperidino)carbonyl]biphenyl

(5) 4-aminomethyl-4'-methoxy-3'-[(4-methoxycarbonyl-butyl)aminosulphonyl]biphenyl
R_f value: 0.17 (silica gel; methylene chloride/methanol = 15:1)

(6) 4-aminomethyl-4'-methoxy-3'-[(4-methoxycarbonyl-butyl)aminocarbonyl]biphenyl

(7) 4-aminomethyl-3'-[(4-methoxycarbonylcyclohexyl)-aminocarbonyl]biphenyl

(8) 4-aminomethyl-4'-hydroxy-3'-[N-(4-methoxycarbonyl-cyclohexyl)-N-methyl-aminocarbonyl]-biphenyl

hydrochloride

Melting point: 220°C (from 160°C sintering, from 180°C decomp.)

R_f value: 0.30 (silica gel; methylene chloride/methanol/concentrated ammonia = 9:1:0.1)

(9) 4-aminomethyl-4'-methoxy-3'-[(4-methoxycarbonyl-cyclohexyl)-aminocarbonyl]-biphenyl

Example 11

3-(5-Carboxyvalerylamino)-3'-guanidinobiphenyl

Prepared by refluxing 3-amino-3'-[(5-carboxy-valeryl)amino]biphenyl hydrochloride with cyanamide in dioxane for 3 hours.

The following compound is obtained analogously:

(1) 3-guanidino-3'-(5-methoxycarbonylvalerylamino)-biphenyl

Example 12

4-Cyano-4'-[[[3-(2-methoxycarbonylethyl)phenyl]-aminocarbonyl]methyl]biphenyl

---

A solution of 1.4 g of dicyclohexylcarbodiimide in 20 ml of tetrahydrofuran is added dropwise, whilst cooling with ice, to a mixture of 1 g of 4'-cyano-biphenylyl-4-acetic acid, 1.2 g of methyl 3-(3-aminophenyl)propionate, 0.57 g of 1-hydroxy-1H-benzotriazole-hydrate and 100 ml of tetrahydrofuran. The mixture is stirred for a further hour, allowed to come to ambient temperature and the dicyclohexylurea precipitated is filtered off. The filtrate is evaporated down and the residue is purified by chromatography on silica gel (eluant: methylene

chloride/methanol = 30:1).
Yield: 1.58 g (95% of theory),
Melting point: 166-168°C

The following compounds are obtained analogously:

(1) 4-cyano-4'-[[3-(2-methoxycarbonylethyl)phenyl]-aminocarbonyl]biphenyl
Melting point: 129-132°C

(2) 4-cyano-4'-[[[3-(methoxycarbonylmethyl)phenyl]-aminocarbonyl]methyl]biphenyl
Melting point: 142-144°C

(3) 4-cyano-4'-[[3-(methoxycarbonylmethyl)phenyl]-aminocarbonyl]biphenyl
(Dimethylformamide is used as solvent)
Melting point: 148-149°C

(4) 4-cyano-4'-[(methoxycarbonylmethyloxy)-methylcarbonylamino]biphenyl

(5) 4-cyano-4'-[[N-(methoxycarbonylmethyl)-N-methyl-amino]methylcarbonylamino]biphenyl

(6) 4-cyano-4'-[(4-methoxycarbonylmethylpiperidino)-carbonyl]biphenyl
Melting point: 130-134°C

(7) 4-cyano-4'-[(3-methoxycarbonylmethylpiperidino)-carbonyl]biphenyl
Melting point: 130-134°C

(8) 4-cyano-4'-[(3-methoxycarbonylmethylpiperidino)-carbonylmethyl]biphenyl
R_f value: 0.71 (silica gel; methylene chloride/ethanol = 9:1)

(9) 4-cyano-4'-[(4-methoxycarbonylmethylpiperidino)-carbonylmethyl]biphenyl
Melting point: 116-118°C

(10) 4-cyano-4'-[(4-methoxycarbonylbutyl)-aminocarbonyl]biphenyl
Melting point: 148-150°C

(11) 4-cyano-4'-[[4-(2-methoxycarbonylethyl)-piperazino]carbonyl]biphenyl
R_f value: 0.62 (silica gel; methylene chloride/ethanol = 9:1)

(12) 4-cyano-4'-[(4-methoxycarbonylmethylpiperazino)-carbonyl]biphenyl
Melting point: 170-172°C

(13) 4-cyano-4'-[(4-methoxycarbonylcyclohexyl)-aminocarbonyl]biphenyl
Melting point: 273-275°C (decomp.)

(14) 4-(N-benzyloxycarbonylamidino)-4'-[[[2-benzyloxy-carbonyl-1-[[2-(4-methoxyphenyl)ethyl]aminocarbonyl]-ethylamino]carbonylmethyl]aminocarbonyl]biphenyl
Melting point: 162-165°C

In order to prepare 4'-(N-benzyloxycarbonylamidino)-biphenyl-4-carboxylic acid, the starting material used is methyl 4'-cyano-biphenyl-4-carboxylate, which is converted analogously to Example 6 into methyl 4'-amidino-biphenyl-4-carboxylate. The latter is converted into the N-benzyloxycarbonyl derivative by reacting it in a 4:1 mixture of methylene chloride and methanol in the presence of 1N sodium hydroxide solution with benzylchloroformate. The saponification of the methylester to obtain the carboxylic acid is carried out using lithium hydroxide.

Glycyl-aspartic acid-β-benzylester-α-[2-(4-methoxyphenyl)ethyl]amide is prepared by known methods of peptide synthesis, by first condensing β-benzyl-N-tert-butyloxycarbonyl-aspartate with 2-(4-methoxyphenyl)ethylamine, according to Example 15, then removing the protection from the amino function of the aspartic acid part and reacting the product with N-tert-butyloxycarbonyl-glycine, again analogously to Example 15, and again removing the protection.

(15) 4-cyano-4'-hydroxy-3'-[N-(4-methoxycarbonyl-cyclohexyl)-N-methyl-aminocarbonyl]-biphenyl
R_f value: 0.40 (silica gel; cyclohexane/ethyl acetate = 7:3)

(16) 4-cyano-4'-[N-(4-methoxycarbonyl-cyclohexyl)-N-methyl-aminocarbonyl]-biphenyl
Melting point: 218-220°C

Example 13

4-Cyano-4'-(5-ethoxycarbonylpentyloxy)biphenyl

1.95 g of 4-cyano-4'-hydroxy-biphenyl are dissolved in 25 ml of dimethylformamide. 0.44 g of a 55% dispersion of sodium hydride in oil is added to the mixture which has been cooled to 0°C and the resulting mixture is stirred for 0.5 hours. 1.28 g of 6-bromo-caproic acid and a further 10 ml of dimethylformamide are added and the mixture is stirred for 2 hours at ambient temperature. The dimethylformamide is distilled off in vacuo, the residue is triturated with water, the precipitate formed is filtered off and recrystallised from ethanol.
Yield: 2.1 g (62% of theory),
Melting point: sinters from 62°C

Calculated:	C	74.75	H	6.87	N 4.15
Found:		74.40		6.76	4.24

The following compounds are obtained analogously:

(1) 4-cyano-4'-(3-methoxycarbonylpropyloxy)biphenyl
Melting point: 107-108°C

(2) 4-cyano-4'-(4-methoxycarbonylbutyloxy)biphenyl
Melting point: 97-99°C

(3) 4-cyano-4'-(5-ethoxycarbonylpentyloxy)-3'-nitro-biphenyl

(4) 4-cyano-4'-(4-methoxycarbonylbutylthio)biphenyl

(5) 3-chloro-4-cyano-4'-(5-ethoxycarbonylpentyloxy)-biphenyl

(6) 4-cyano-4'-(5-ethoxycarbonylpentyloxy)-3-fluoro-biphenyl

(7) 4-cyano-2',3'-dimethyl-4'-(5-ethoxycarbonyl-pentyloxy)biphenyl

(8) 4-cyano-4'-(5-ethoxycarbonylpentyloxy)-3'-trifluoromethylbiphenyl

(9) 4-cyano-4'-[[(2-methoxycarbonylethyl)-aminocarbonyl]methyloxy]biphenyl
(4-cyano-4'-[[[N-(2-methoxycarbonylethyl)-N-methyl-amino]carbonyl]methyloxy]biphenyl is obtained from 4-cyano-4'-[[(2-methoxycarbonylethyl)aminocarbonyl]-methyloxy]biphenyl by methylation with methyliodide)

(10) 4-[2-[N-acetyl-N-(2-methoxycarbonylethylamino)-ethyloxy]-4'-cyano-biphenyl

(11) 4-cyano-4'-[2-[N-(2-methoxycarbonylethyl)-N-methanesulphonylamino]ethyloxy]biphenyl

(12) 4-[2-[N-benzoyl-N-(2-methoxycarbonylethyl)amino]-ethyloxy]-4'-cyano-biphenyl

(13) 4-cyano-4'-[(methoxycarbonylmethylaminocarbonyl)-methyloxy]biphenyl

(14) 4-cyano-4'-[N-[(methoxycarbonylmethyl-aminocarbonyl)methyl]-N-methylamino]biphenyl
(Ethyldiisopropylamine was used as the base)

(15) 4-cyano-4'-[N-[[N-(2-methoxycarbonylethyl)-N-methylamino]carbonyl]-N-methylamino]biphenyl
(prepared from 4-cyano-4'-[[(2-methoxycarbonylethyl)-aminocarbonyl]amino]biphenyl by methylation with methyliodide)

(16) 4-cyano-4'-[[(4-methoxycarbonylpiperidino)-carbonyl]methyloxy]biphenyl

(17) 4-cyano-4'-(5-methoxycarbonylpentyloxy)-3'-methylthio]biphenyl

(18) 4-cyano-4'-[N-(3-methoxycarbonylpropionyl)-N-methylamino]biphenyl
(prepared from 4-cyano-4'-[(3-methoxycarbonyl-propionyl)amino]biphenyl by methylation with methyliodide)

(19) 4-cyano-4'-[N-(4-methoxycarbonylbutyryl)-N-methylamino]biphenyl
(prepared from 4-cyano-4'-[(4-methoxycarbonylbutyryl)-amino]biphenyl by methylation with methyliodide)

(20) 4-cyano-4'-[[N-(3-methoxycarbonylpropyl)-N-methylamino]sulphonyl]biphenyl
(prepared from 4-cyano-4'-[(3-methoxycarbonylpropyl)-aminosulphonyl]biphenyl by methylation with

methyliodide)

(21) 4-cyano-4'-[N-(4-methoxycarbonylbutyryl)-N-methylamino]biphenyl
(prepared from 4-cyano-4'-(4-methoxycarbonyl-butyrylamino)biphenyl by methylation with methyliodide)

(22) 4-cyano-4'-[[(2-methoxycarbonylethyl)thiomethyl]-carbonyl]biphenyl
(prepared from 4-bromoacetyl-4'-cyano-biphenyl and methyl 3-mercaptopropionate)

(23) 4-cyano-4'-[2-(methoxycarbonylmethylthio)ethyl]-biphenyl
(prepared analogously to (22))

(24) 4-cyano-4'-[(3-methoxycarbonylpropyl)thiomethyl]-biphenyl
(prepared analogously to (22))

Example 14

4-Cyano-4'-[[(3-ethoxycarbonylpiperidino)carbonyl]-methyloxy]biphenyl

---

5.35 g of carbonyldiimidazole are added to a solution of 7.6 g of 4-(carboxymethyloxy)-4'-cyano-biphenyl (prepared from 4-cyano-4'-hydroxy-biphenyl and tert.butyl bromoacetate according to Example 13, but with potassium tert.butoxide as base, and subsequent ester cleaving with trifluoroacetic acid) in 30 ml of tetrahydrofuran and the resulting mixture is stirred for 0.5 hours at ambient temperature. 5.1 ml of ethyl piperidine-3-carboxylate are added and the mixture is stirred for 22 hours at ambient temperature. The tetrahydrofuran is evaporated off, the residue is taken up in ethyl acetate and washed successively with saturated sodium bicarbonate solution, 0.1N hydrochloric

acid and water. After evaporation of the organic phase the residue remains as an oil.
Yield: 10.5 g (89% of theory),
Calculated: C 70.39 H 6.16 N 7.14
Found: 70.12 6.45 7.14

The following compounds are obtained analogously:

(1) 4-cyano-4'-[[(4-ethoxycarbonylpiperidino)-carbonyl]methyloxy]biphenyl
Melting point: 98-100°C

(2) 4-cyano-4'-[(4-methoxycarbonylmethylpiperidino)-carbonyl]biphenyl
Melting point: 124-125°C,
R_f value: 0.61 (silica gel; methylene chloride/ethanol = 1:1)

(3) 4-cyano-4'-[(3-ethoxycarbonylmethylpiperidino)-carbonyl]biphenyl

(4) 4-cyano-4'-[(3-methoxycarbonylmethylpyrrolidino)-carbonyl]biphenyl

(5) 4-cyano-4'-[(4-ethoxycarbonylpiperidino)-carbonylmethyl]biphenyl

(6) 4-cyano-4'-[(3-ethoxycarbonylmethylpiperidino)-carbonylmethyl]biphenyl

(7) 4-cyano-4'-[(3-methoxycarbonylmethylpyrrolidino)-carbonylmethyl]biphenyl

(8) 4-cyano-4'-[(3-ethoxycarbonylpiperidino)-carbonylmethyl]biphenyl

(9) 4-(N-benzyloxycarbonylamidino)-4'-[(4-

benzoyloxycarbonylmethyl-4-hydroxy-piperidino)-carbonyl]biphenyl

(10) 4-cyano-4'-[(4-methoxycarbonylmethylene-piperidino)carbonyl]biphenyl

(11) 4-cyano-4'-[(4,4-bis-methoxycarbonylmethyl-piperidino)carbonyl]biphenyl

(12) 4-cyano-4'-[(4-sulphomethylpiperidino)carbonyl]-biphenyl

(13) 4-cyano-4'-[[4-(5-tetrazolylmethyl)piperidino]-carbonyl]biphenyl

Example 15

4-Cyano-4'-[(2-ethoxycarbonylethylamino)carbonyl]-biphenyl

A mixture of 2 g of 4'-cyano-biphenylyl-4-acetic acid, 1.9 ml of N-methyl-morpholine and 100 ml of tetrahydrofuran is cooled to -30°C and 1.1 ml of isobutyl-chloroformate are added. The mixture is stirred for one hour, 1.3 g of β-alanine-ethylester hydrochloride are added and the resulting mixture is stirred for a further 50 hours at ambient temperature. The resulting solution is stirred into 300 ml of 0.5 molar potassium hydrogen sulphate solution and extracted with ethyl acetate. The ethyl acetate phase is concentrated by evaporation and ether is added, whereupon the product is obtained in crystalline form.
Yield: 1.1 g (39% of theory),
Melting point: 132-136°C

The following compounds are obtained analogously:

(1) 4-cyano-4'-[(3-ethoxycarbonylpropylamino)carbonyl]-

biphenyl

(2) 4-cyano-4'-[[(2-ethoxycarbonylethylamino)carbonyl]-biphenyl

(3) 4-cyano-4'-[[N-(3-methoxycarbonyl-2-propenyl)-N-methylamino]carbonyl]biphenyl

(4) 4-[[2-benzyloxycarbonyl-1-[[2-(4-methoxyphenyl)-ethyl]aminocarbonyl]ethylamino]carbonylmethyl]-4'-cyano-biphenyl

(5) 4-cyano-4'-[(4-ethoxycarbonylmethylpiperidino)-carbonyl]biphenyl
Melting point: 118-120°C

(6) 4-cyano-4'-[(4-dimethylaminocarbonylmethyl-piperidino)carbonyl]biphenyl

Example 16

4-Cyano-4'-(4-methoxycarbonylbutyrylamino)biphenyl

6.6 g of 4-amino-4'-cyano-biphenyl (melting point: 171-173°C, prepared by reduction of 4-cyano-4'-nitro-biphenyl with hydrogen in the presence of palladium/charcoal in ethyl acetate, 4-cyano-4'-nitro-biphenyl is prepared by reacting 4-cyano-biphenyl with fuming nitric acid) and 5.8 g of N-ethyl-diisopropylamine are dissolved in 70 ml of methylene chloride and 5.6 g of glutaric acid monomethylester chloride are added with stirring. The mixture is stirred for two hours at ambient temperature. The organic phase is washed successively with 0.1N sodium hydroxide solution, 0.1N hydrochloric acid and water. After evaporation of the organic phase the residue is recrystallised from ethanol.
Yield: 7.5 g (68% of theory),

Melting point: 153-155°C

The following compounds are obtained analogously:

(1) 3-amino-3'-(5-methoxycarbonylvalerylamino)biphenyl

(2) 3-bromo-4'-cyano-4-(4-methoxycarbonylbutyrylamino)-biphenyl
(This compound may also be obtained by bromination of 4-cyano-4'-(4-methoxycarbonylbutyrylamino)biphenyl with bromine in glacial acetic acid)

(3) 4-cyano-3',5'-dibromo-4'-(4-methoxycarbonyl-butyrylamino)biphenyl

(4) 3-acetylamino-4'-cyano-4-(5-methoxycarbonyl-pentyloxy)biphenyl

(5) 3-benzoylamino-4'-cyano-4-(5-methoxycarbonyl-pentyloxy)biphenyl

(6) 4-cyano-3'-methanesulphonylamino-4'-(5-methoxycarbonylpentyloxy)biphenyl

(7) 3-benzenesulphonylamino-4'-cyano-4-(5-methoxycarbonylpentyloxy)biphenyl

(8) 4-cyano-4'-[(3-methoxycarbonylpropyl)-aminosulphonyl]biphenyl

(9) 4-cyano-4'-methoxy-3'-[(4-methoxycarbonylbutyl)-aminosulphonyl]biphenyl
(Prepared from the trimethylsilyl-5-trimethylsilylamino-valerate produced as an intermediate product and subsequent esterification with methanolic hydrochloric acid)
R_f value: 0.31 (silica gel; methylene chloride/methanol

= 15:1)

Example 17

4-Cyano-4'-[(4-methoxycarbonylbutyl)sulphonyl]biphenyl

At 90°C, 30% hydrogen peroxide is slowly added to a solution of 4-cyano-4'-(4-methoxycarbonyl-butylthio)-biphenyl in a 10:6 mixture of acetic anhydride and glacial acetic acid. The mixture is stirred for another hour, poured onto ice water, neutralised and extracted with ethyl acetate. The ethyl acetate phases are evaporated down and the residue is purified by column chromatography.

The following compounds are obtained analogously:

(1) 4-cyano-4'-[(3-methoxycarbonylpropyl)-sulphonylmethyl]biphenyl

(2) 4-cyano-4'-(5-methoxycarbonylpentyloxy)-3'-methylsulphonylbiphenyl

Example 18

3-Amino-4'-cyano-4-(5-methoxycarbonylpentyloxy)biphenyl

Prepared from 4-cyano-4'-(5-methoxycarbonyl-pentyloxy)-3'-nitro-biphenyl by hydrogenating with hydrogen under 5 bars of pressure in methanol in the presence of 10% palladium/charcoal at ambient temperature.

Example 19

4-Cyano-4'-[(4-methoxycarbonylmethylpiperidino)-methyl]-biphenyl

---

Prepared by alkylating methyl piperidyl-4-acetate with 4-bromomethyl-4'-cyano-biphenyl in dimethyl-formamide in the presence of diisopropylethylamine.

The following compounds are obtained analogously:

(1) 4-cyano-4'-[(3-methoxycarbonylmethylpiperidino)-methyl]biphenyl

(2) 4-cyano-4'-[2-(4-methoxycarbonylpiperidino)ethyl]-biphenyl

(3) 4-cyano-4'-[2-(3-methoxycarbonylmethylpiperidino)-ethyl-biphenyl

(4) 4-cyano-4'-[(3-methoxycarbonylmethylpyrrolidino)-methyl]biphenyl

(5) 4-cyano-4'-[2-(3-methoxycarbonylmethylpyrrolidino)-ethyl]biphenyl

(6) 4-cyano-4'-[2-(3-methoxycarbonylpiperidino)ethyl]-biphenyl

Example 20

4-Cyano-4'-[(2-ethoxycarbonylethylaminocarbonyl)amino]-biphenyl

---

Prepared by reacting 4-amino-4'-cyano-biphenyl with ethyl 3-isocyanato-propionate in dioxane at 50°C.

Example 21

4-Cyano-4'-[(2-ethoxycarbonylethyl)amino-sulphonylamino]biphenyl

---

0.68 g of 4-amino-4'-cyano-biphenyl and 1.1 g of 2-[(2-ethoxycarbonylethyl)aminosulphonyloxy]phenol are heated in 5 ml of dimethylformamide to 80°C for 15 hours. The dimethylformamide is distilled off in vacuo and the residue is taken up in ethyl acetate. After washing with water, the organic phase is evaporated down and the residue remaining is purified by column chromatography (silica gel; eluant: cyclohexane/ethyl acetate = 7:3).

Yield: 0.8 g (62% of theory),

R_f value: 0.19 (silica gel; cyclohexane/ethyl acetate = 7:3)

Example 22

Dry ampoule containing 2.5 mg of active substance per 1 ml

Composition:

Active substance	2.5 mg
Mannitol	50.0 mg
Water for injections ad	1.0 ml

Preparation:

The active substance and mannitol are dissolved in water. After transferring the solution to the ampoule, it is freeze-dried.

At the point of use, the solution is made up with water for injections.

Example 23

Dry ampoule containing 35 mg of active substance per 2 ml

Composition:

Active substance	35.0 mg
Mannitol	100.0 mg
Water for injections ad	2.0 ml

Preparation:

The active substance and mannitol are dissolved in water. After transferring the solution to the ampoule, it is freeze-dried.

At the point of use, the solution is made up with water for injections.

Example 24

Tablet containing 50 mg of active substance

Composition:

(1) Active substance	50.0 mg
(2) Lactose	98.0 mg
(3) Corn starch	50.0 mg
(4) Polyvinylpyrrolidone	15.0 mg
(5) Magnesium stearate	2.0 mg
	215.0 mg

Preparation:

Components (1), (2) and (3) are mixed together and granulated with an aqueous solution of component (4). Component (5) is added to the dried granules. From this mixture, compressed tablets are produced, biplanar,

facetted on both sides and notched on one side.
Diameter of tablets: 9 mm.

Example 25

Tablet containing 350 mg of active substance

Composition:

(1) Active substance	350.0 mg
(2) Lactose	136.0 mg
(3) Corn starch	80.0 mg
(4) Polyvinylpyrrolidone	30.0 mg
(5) Magnesium stearate	4.0 mg
	600.0 mg

Preparation:

Components (1), (2) and (3) are mixed together and granulated with an aqueous solution of component (4). Component (5) is added to the dried granules. From this mixture, compressed tablets are produced, biplanar, facetted on both sides and notched on one side.
Diameter of tablets: 12 mm.

Example 26

Capsules containing 50 mg of active substance

Composition:

(1) Active substance	50.0 mg
(2) Dried corn starch	58.0 mg
(3) Powdered lactose	50.0 mg
(4) Magnesium stearate	2.0 mg
	160.0 mg

Preparation:

Component (1) is triturated with component (3). This triturate is added to the mixture of components (2) and (4), with thorough mixing.

This powdered mixture is packed into size 3 hard gelatin oblong capsules in a capsule filling machine.

Example 27

Capsules containing 350 mg of active substance

Composition:

(1) Active substance	300.0 mg
(2) Dried corn starch	46.0 mg
(3) Powdered lactose	30.0 mg
(4) Magnesium stearate	4.0 mg
	430.0 mg

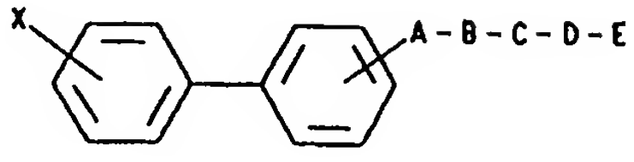
Preparation:

Component (1) is triturated with component (3). This triturate is added to the mixture of components (2) and (4), with thorough mixing.

This powdered mixture is packed into size 0 hard gelatin oblong capsules in a capsule filling machine.

Claims

1. Compounds of formula I



(I)

(wherein
one of the rings of the biphenyl moiety may be mono- or disubstituted by a group R_1 and the other may be mono- or disubstituted by a group R_2,

R_1 and R_2, which may be identical or different, each represents a halogen atom or a naphthyl, alkyl, hydroxy, trifluoromethyl, amino, nitro, alkoxy, alkylsulphenyl, alkylsulphinyl, alkylsulphonyl, alkylcarbonylamino, N-alkyl-alkylcarbonylamino, arylcarbonylamino, N-alkyl-arylcarbonylamino, alkylsulphonylamino or N-alkyl-alkylsulphonylamino group or an arylsulphonylamino or N-alkyl-arylsulphonylamino group wherein the aryl moiety may contain a phenyl ring optionally mono-, di- or trisubstituted by halogen atoms or hydroxy, amino, alkyl, alkoxy, alkylsulphenyl, alkylsulphinyl, alkylsulphonyl, alkylcarbonylamino and alkylsulphonylamino groups;

X represents a cyano group or an amino, aminoalkyl, amidino, guanidino or guanidinoalkyl group, wherein one of the hydrogen atoms at one of the nitrogen atoms may be replaced by a hydroxy, amino or cyano group, by a C_{1-3}-alkoxy group, by a C_{1-4}-alkyl group, by a C_{2-5} (alkoxycarbonyl) group, by a phenyl(C_{1-3}alkoxy)-carbonyl group, or by a phenyloxycarbonyl, benzoyl, (C_{1-3}alkyl)-carbonyl or phenyl(C_{1-3}alkyl)carbonyl group, wherein any phenyl group is optionally mono- or disubstituted by a

group R_1 or R_2;

A represents a bond, an oxygen or sulphur atom or an $-NR_3-CO-$, $-CO-NR_3-$, $-NR_4-$, $-SO-$, $-SO_2-$, $-CO-$, $-SO_2-NR_3-$, $-NR_3-SO_2-$, $-NR_3-CO-NR_3-$ or $-NR_3-SO_2-NR_3-$ group;

B represents a bond, a straight-chained or branched C_{1-6}-alkylene group which may be mono- or polyunsaturated, although a double bond may not be directly linked to an oxygen, sulphur or phosphorus atom of groups A, C or E and a triple bond may not be directly linked to a heteroatom of groups A, C or E, or B may represent a C_{3-7}-cycloalkylene group or a phenylene or naphthylene group which may be mono-, di- or trisubstituted in the aromatic nucleus by halogen atoms, amino, hydroxy, C_{1-3}-alkyl or C_{1-3}-alkoxy groups;

C represents a bond, a $-CO-$, $-CO-NR_3-$, $-CO-NR_3-(CH_2)_n-R_5CR_6-$, $-CO-NR_3-(CH_2)_n-NR_5-$ or $-CO-NR_3-(CH_2)_n-CR_5=CH-$ group, or, if a heteroatom of group A is not bound to the same carbon atom of group B as is group C, C may represent an oxygen or sulphur atom, an $-SO-$, $-SO_2-$, $-NR_4-$, $-NR_3-CO-$ or $-NR_3-(CH_2)_n-CHR_5-$ group, although an oxygen or sulphur atom of group C cannot directly follow an oxygen or sulphur atom or a $-CO-$ group of group A and an oxygen atom or a sulphenyl or sulphinyl group of group C cannot directly follow a nitrogen atom of group A and a $-CO-$ group of group C cannot directly follow an oxygen or sulphur atom or a $-CO-NR_3-$ group of group A;

D represents a bond, a straight-chained or branched C_{1-4}-alkylene group which may be mono- or polyunsaturated, although a double bond may not be bound directly to an oxygen, sulphur or phosphorus atom of groups A, C or E or to a triple bond of group B and a triple bond may not be directly linked to a heteroatom of groups A, C or E

or to a double or triple bond of group B, or D may represent a phenylene or (C_{1-3}-alkylene)phenylene group optionally mono-, di- or trisubstituted in the phenyl nucleus by halogen atoms, amino, hydroxy, C_{1-3}-alkyl or C_{1-3}-alkoxy groups;

E represents a carboxy, sulpho, phosphono, 5-tetrazolyl, O-(C_{1-3}alkyl)-phosphono or $(R_3)_2NCO$- group or a C_{2-6}-(alkoxy-carbonyl) group wherein the alkoxy moiety may be substituted in the 1-, 2- or 3-position by a phenyl group (itself optionally mono- or disubstituted by groups R_1 or R_2) or by a pyridyl group or in the 2- or 3-position by a pyrrolidino, piperidino, hexamethyleneimino, 2-oxo-1-pyrrolidinyl, morpholino, thiomorpholino, 1-oxido-thiomorpholino or 1,1-dioxidothiomorpholino group or by a piperazino group itself optionally substituted in the 4-position by a group R_5;

n represents the number 0, 1 or 2,

R_3 represents a hydrogen atom or an optionally phenyl-substituted C_{1-3}-alkyl group, wherein the phenyl group is itself optionally mono- or disubstituted by groups R_1 or R_2;

R_4 represents a hydrogen atom, an optionally phenyl-substituted C_{1-3}-alkyl group, a formyl group, a carbonyl or sulphonyl group substituted by a C_{1-3}-alkyl group, by a phenyl(C_{1-3}-alkyl) group or by a phenyl group, wherein the phenyl groups may be mono- or disubstituted by groups R_1 or R_2; and

R_5 represents a hydrogen atom or a C_{1-3}-alkyl group or a $-CO-NR_3-(C_{1-3}$-alkylene)-phenyl group in which the phenyl group may be mono- or disubstituted by groups R_1 or R_2, or if group C is substituted by the groups R_3 and R_5, then R_5 together with R_3 may represent a C_{2-4}-alkylene group; and

R_6 represents a hydrogen atom or a hydroxy, carboxyalkyl or alkoxycarbonylalkyl group;

whilst at least one of the groups A, B, C and D does not represent a bond, group E cannot directly follow a heteroatom of groups A or C and, if X represents an aminoalkyl group, the shortest distance between the NH_2 group and group E is at least 12 bonds, and each alkyl, alkylene or alkoxy moiety unless otherwise specified contains 1 to 3 carbom atoms) and the stereoisomers and the salts thereof.

2. Compounds of formula I as claimed in claim 1, wherein one of the rings of the biphenyl moiety may be substituted by R_1 and the other may be substituted by R_2 where R_1 and R_2, which may be identical or different, each represents a fluorine, chlorine or bromine atom, or an alkyl, hydroxy, trifluoromethyl, amino, nitro, alkoxy, alkylsulphenyl, alkylsulphinyl, alkylsulphonyl, alkylcarbonylamino, benzoylamino, alkylsulphonylamino or phenylsulphonylamino group,

or wherein one of the rings of the biphenyl moiety may be disubstituted by R_1 and the other by R_2 where R_1 and R_2, which may be identical or different, each represents a C_{1-3}-alkyl group or a chlorine or bromine atom;

X represents a cyano group, an amino(C_{1-3}-alkyl), amino, amidino or guanidino group wherein one of the hydrogen atoms at one of the nitrogen atoms in these groups may be substituted by an amino group, by a C_{1-4}-alkyl group, by a C_{1-3}-alkoxy, by a C_{2-5}(alkoxycarbonyl) group, or by a benzyloxycarbonyl, 1-phenylethoxycarbonyl, 2-phenylethoxycarbonyl or phenyloxycarbonyl group;

A represents a bond, an oxygen or sulphur atom or an $-NR_3-CO-$, $-CO-NR_3-$, $-NR_4-$, $-SO-$, $-SO_2-$, $-CO-$, $-SO_2-NR_3-$, $-NR_3-CO-NR_3-$ or $-NR_3-SO_2-NR_3-$ group;

B represents a bond, a straight-chained or branched C_{1-6}-alkylene group or a C_{3-5}-alkenylene or C_{3-5}-alkynylene group although a double bond may not be linked directly to an oxygen, sulphur or phosphorus atom of groups A, C or E and a triple bond may not be directly linked to a heteroatom of groups A, C or E, or B may represent a cyclohexylene or phenylene group;

C represents a bond, a $-CO-NR_3-$, $-CO-NR_3-(CH_2)_n-R_5CR_6-$, $-CO-NR_3-(CH_2)_n-NR_5-$, or $-CO-NR_3-(CH_2)_n-CR_5=CH-$ group, or, if a heteroatom of group A is not bound to the same carbon atom of group B as is group C, C may also represent an oxygen or sulphur atom or an $-SO-$, $-SO_2-$, $-NR_4-$, $-NR_3-CO-$ or $-NR_3-(CH_2)_n-CHR_5-$ group although generally an oxygen or sulphur atom of group C cannot directly follow an oxygen or sulphur atom or a $-CO-$ group of group A, and an oxygen or sulphenyl or sulphinyl group of group C cannot directly follow a nitrogen atom of group A, and a $-CO-$ group of group C cannot directly follow an oxygen or sulphur atom or a $-CO-NR_3-$ group of group A;

D represents a bond, a straight-chained or branched C_{1-4}-alkylene group or a phenylene or (C_{1-3}-alkylene)phenylene;

E represents a carboxy, sulpho, phosphono, 5-tetrazolyl, O-(C_{1-3}alkyl)-phosphono or $(R_3)_2NCO-$ group or a C_{2-5}(alkoxy-carbonyl) group wherein the alkoxy moiety may be substituted in the 1-, 2- or 3-position by a phenyl or pyridyl group or the alkoxy moiety may be substituted in the 2- or 3-position by a 2-oxo-1-pyrrolidinyl, morpholino, thiomorpholino or 1-oxido-thiomorpholino group;

n represents the number 0, 1 or 2;

R_3 represents a hydrogen atom or a C_{1-3}-alkyl group;

R_4 represents a hydrogen atom, a C_{1-3}-alkyl group or a carbonyl or sulphonyl group substituted by a C_{1-3}-alkyl group or by a phenyl group;

R_5 represents a hydrogen atom or a C_{1-3}-alkyl group or a $-CO-NR_3-(C_{1-3}$-alkylene)-phenyl group wherein the phenyl moiety may be substituted by one or two C_{1-3}-alkoxy groups or, if the group C is substituted by the groups R_3 and R_5, then R_5 together with R_3 may represent a C_{2-4}-alkylene group; and

R_6 represents a hydrogen atom or a hydroxy, carboxyalkyl or alkoxycarbonylalkyl group;

at least one of the groups A, B, C and D does not represent a bond, group E cannot directly follow a heteroatom of group A or C and, if X represents an aminoalkyl group, the shortest distance between the NH_2 group and group E is at least 12 bonds, and each alkyl, alkylene or alkoxy moeity unless otherwise specified contains 1 to 3 carbon atoms;

and the stereoisomers and the salts thereof.

3. Compounds of formula I as claimed in claim 1, wherein

the phenyl group linked to the group X is substituted by a fluorine, chlorine or bromine atom;

the phenyl ring linked to the group A is substituted by a fluorine or chlorine atom or by a hydroxy, methoxy, trifluoromethyl, methylsulphenyl, methylsulphinyl, methylsulphonyl, nitro, amino, acetylamino, benzoylamino, methanesulphonylamino or benzenesulphonyl-

amino group or the phenyl ring linked to group A is substituted by one or two methyl groups or by one or two bromine atoms;

X represents an aminomethyl, amidino or guanidino group wherein a hydrogen atom at one of the nitrogen atoms may be replaced by a C_{1-4}-alkyl group, or by a methoxycarbonyl, ethoxycarbonyl or benzyloxycarbonyl group;

A represents a bond, an oxygen or sulphur atom or an -NH-CO-, $-NCH_3$-CO-, -CO-NH-, $-CO-NCH_3$-, $-NCH_3$, -SO-, $-SO_2$-, $-SO_2$-NH-, $-SO_2-NCH_3$-, -CO-, -NH-CO-NH-, $-NH-SO_2$-NH- or $-NCH_3$-CO-NCH_3- group;

B represents a bond, a straight-chained or branched C_{1-5}-alkylene group, a straight-chained or branched C_3-alkenylene group in which the double bond cannot be directly linked to an oxygen, sulphur or phosphorus atom of groups A, C or E, or B represents a cyclohexylene or phenylene group;

C represents a bond, a -CO-NH-, $-CO-NCH_3$-, $-CO-NH-(CH_2)_2-CH(CH_2-COOH)-$, $-CO-NCH_3-(CH_2)_2-CH(CH_2-COOH)-$, $-CO-NH-(CH_2)_2-CH(CH_2-COOCH_3)-$, $-CO-NCH_3-(CH_2)_2-CH(CH_2-COOCH_3)-$, pyrrolidinylene-N-carbonyl, piperidinylene-N-carbonyl or piperazinylene-N-carbonyl group, a 4-methanylylidene-piperidinocarbonyl group wherein the group -D-E is bound to the methanylylidene moiety, a 4-hydroxy-4-piperidinylene-N-carbonyl, 4-carboxymethyl-4-piperidinylene-N-carbonyl or 4-methoxycarbonylmethyl-4-piperidinylene-N-carbonyl group wherein the group -D-E is bound to the 4-position, or a [[[2-(methoxyphenyl)-ethyl]-aminocarbonyl]-methylene]-aminocarbonyl group wherein the group -D-E is bound to the methylene carbon atom, or, if a heteroatom of group A is not bound to the same carbon atom of group B as is group C, C may also

represent an oxygen or sulphur atom, an -SO-, $-SO_2-$, -NH-, $-NCH_3-$, $-N(COCH_3)-$, -N(benzoyl)-, $-N(SO_2CH_3)-$, -NH-CO-, 1-pyrrolidinylene or 1-piperidinylene group, although generally an oxygen or sulphur atom of group C cannot directly follow an oxygen or sulphur atom or a -CO- group of group A, and an oxygen or sulphenyl or sulphinyl group of group C cannot directly follow a nitrogen atom of group A, and a -CO- group of group C cannot directly follow an oxygen or sulphur atom or a -CO-NH- or $-CO-NCH_3-$ group of group A;

D represents a bond, a straight-chained or branched C_{1-3}-alkylene group or a (C_{1-2}-alkylene)phenylene group; and

E represents a carboxy, sulpho, phosphono, 5-tetrazolyl or O-methyl-phosphono group or a C_{2-5}(alkoxycarbonyl) group wherein the alkoxy moiety may be substituted in the 1- or 2-position by a phenyl group, or E may also represent an aminocarbonyl, methylaminocarbonyl or dimethylaminocarbonyl group;

at least one of the groups A, B, C and D does not represent a bond, group E cannot directly follow a heteroatom of groups A or C and, if X represents an aminomethyl group, the shortest distance between the amino group and group E is at least 12 bonds;

and the stereoisomers and salts thereof.

4. Compounds of formula I as claimed in claim 1 wherein

the phenyl ring connected to the group X is unsubstituted and the phenyl ring connected to the group A is substituted by a hydroxy or methoxy group;

X represents an aminomethyl or amidino group in which a

hydrogen atom at one of the nitrogen atoms may be replaced by a methoxycarbonyl, ethoxycarbonyl or benzyloxycarbonyl group;

A represents a bond, an oxygen atom, or an -NH-CO-, -CO-NH-, $-CO-NCH_3-$, $-SO_2-NH-$ or $-NH-SO_2-NH-$ group;

B represents a bond, a straight-chained C_{1-5}-alkylene group or a cyclohexylene or phenylene group;

C represents a bond or, if C does not directly follow an oxygen atom or a -CO-NH- or $-CO-NCH_3-$ group of group A, C may also represent a -CO-NH- group, a piperidinylene-N-carbonyl group linked in the 3- or 4-position to group -D-E, a 4-piperazinylene-N-carbonyl or 4-methanylylidene-piperidinocarbonyl group wherein the group -D-E is bound to the methanylylidene group, or C may represent a 4-hydroxy-4-piperidinylene-N-carbonyl, 4-carboxymethyl-4-piperidinylene-N-carbonyl or 4-methoxycarbonylmethylene-piperidinylene-N-carbonyl group wherein the group -D-E is bound to the 4-position, or C may represent a [[[2-(4-methoxyphenyl)-ethyl]aminocarbonyl]-methylene]-aminocarbonyl group wherein the group -D-E is linked to the methylene carbon atom, or, if C does not directly follow an oxygen atom or a carbonyl group of group A and a heteroatom of group A is not linked to the same carbon atom of B which carries the group C, C may also represent an -NH-CO- group or, if C does not directly follow an oxygen atom of group A and a heteroatom of group A is not linked to the same carbon atom of B which carries group C, C may also represent a 1-piperidinylene group;

D represents a bond or a methylene, ethylene, methylene-phenylene or ethylenephenylene group; and

E represents a carboxyl, methoxycarbonyl,

ethoxycarbonyl, benzyloxycarbonyl, aminocarbonyl, dimethylaminocarbonyl or 5-tetrazolyl group;

whilst at least one of the groups A, B, C and D does not represent a bond and E cannot directly follow a heteroatom of groups A or C, and, if X represents an aminomethyl group, the shortest distance between the amino group and group E is at least 12 bonds;

and the stereoisomers and salts thereof.

5. Compounds of formula I as claimed in claim 1 wherein

the biphenylyl group is unsubstituted;

X is an aminomethyl or amidino group in which a hydrogen atom at one of the nitrogen atoms may be replaced by a methoxycarbonyl or benzyloxycarbonyl group;

A represents a bond, an oxygen atom or an -NH-CO- or -CO-NH- group;

B represents a bond, a straight-chained C_{1-5}-alkylene group or a cyclohexylene group;

C represents a bond or, if C does not directly follow a heteroatom or a carbonyl group of group A, C may represent a -CO-NH- group, a piperidinylene-N-carbonyl group linked in the 3- or 4-position to group -D-E, a piperazinylene-N-carbonyl group wherein group -D-E is bound to the 4-position, or a [[[2-(4-methoxyphenyl)-ethyl]-aminocarbonyl]-methylene]-aminocarbonyl group wherein the group -D-E is linked to the methylene carbon atom;

D represents a bond or a methylene or ethylene group;

and

E represents a carboxyl, methoxycarbonyl, ethoxycarbonyl or benzyloxycarbonyl group;

whilst at least one of the groups A, B, C and D does not represent a bond and E cannot directly follow a heteroatom of groups A or C, and if X represents an aminomethyl group the shortest distance between the amino group and the group E is at least 12 bonds;

and the stereoisomers and salts thereof.

6. A compound as claimed in claim 1 being

4-amidino-4'-[(4-carboxymethylpiperidino)carbonyl]-biphenyl;

4-amidino-4'-[(4-carboxymethylpiperazino)carbonyl]-biphenyl;

4-amidino-4'-[(4-carboxycyclohexyl)aminocarbonyl]-biphenyl;

4-amidino-4'-[(4-methoxycarbonylmethylpiperidino)-carbonyl]biphenyl;

4-amidino-4'-[(4-methoxycarbonylcyclohexyl)-aminocarbonyl]biphenyl; or

4-(N-methoxycarbonylamidino)-4'-[(4-methoxycarbonyl-methylpiperidino)carbonyl]biphenyl;

or a stereoisomer, stereoisomer mixture or salt thereof.

7. A compound as claimed in any one of claims 1 to 6 being a physiologically acceptable addition salt of a

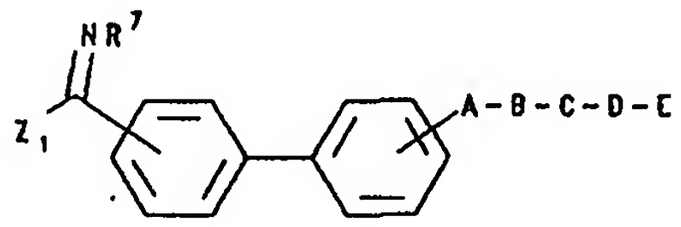
compound of formula I as defined in any of claims 1 to 6.

8. A pharmaceutical composition containing a compound of formula I as claimed in any one of claims 1 to 6 or a physiologically acceptable addition salt thereof together with at least one physiologically acceptable carrier or excipient.

9. Use of a compound of formula I as claimed in any one of claims 1 to 6 or a physiologically acceptable addition salt thereof.

10. A process for preparing compounds as claimed in any one of claims 1 to 7, said process comprising at least one of the following steps:

a) (to prepare compounds of formula I wherein X contains an amidino group) reacting a compound of formula II



(II)

(wherein A, B, C, D and E are as defined in any one of claims 1 to 5,

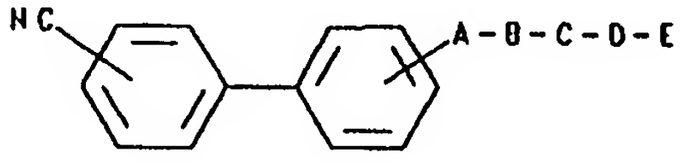
R_7 represents a hydrogen atom or a C_{1-4}-alkyl group and Z_1 represents an alkoxy or aralkoxy group or an alkylthio or aralkylthio group or an amino group) which is optionally formed in the reaction mixture, with an amine of formula III

$$NH_2 - R_8 \qquad (III)$$

(wherein R_8 represents a hydrogen atom, a C_{1-4}-alkyl

group, a hydroxy group, a C_{1-3}-alkoxy group or an amino group) or with an acid addition salt thereof;

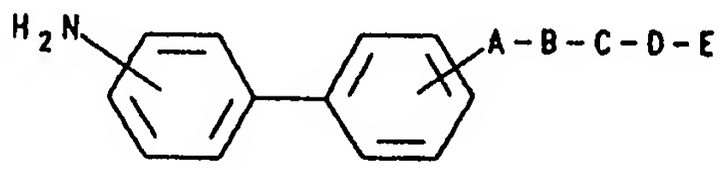
b) (to prepare compounds of formula I wherein X represents an aminomethylene group) reducing a compound of formula IV



(IV)

(wherein A, B, C, D and E are as defined in any one of claims 1 to 5);

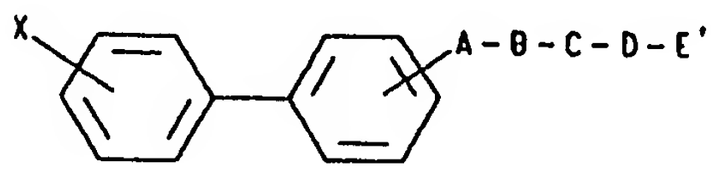
c) (to prepare compounds of formula I wherein X represents a guanidino group) reacting a compound of formula V



(V)

(wherein A, B, C, D and E are as defined in any of claims 1 to 5) or an acid addition salt thereof, with cyanamide;

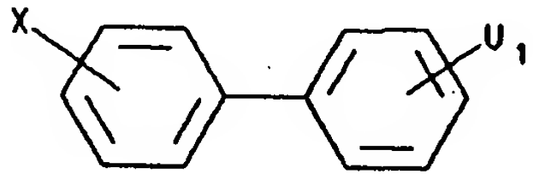
d) (to prepare compounds of formula I wherein E represents a carboxyl group) converting a compound of formula VI



(VI)

(wherein A, B, C, D and X are as defined in any one of claims 1 to 5 and
E', which is bound to a carbon atom, represents a group which can be converted by hydrolysis, treatment with acids, thermolysis or hydrogenolysis into a carboxyl- or bis-(hydroxycarbonyl)methyl group), optionally with subsequent decarboxylation;

e) (to prepare compounds of formula I wherein A represents an $-NR_3-CO-$, $-CO-NR_3-$, $-SO_2-NR_3-$ or $-NR_3-SO_2-$ group) reacting a compound of formula VII



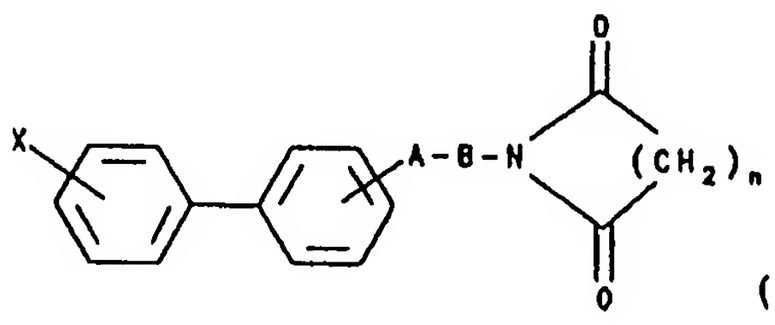
(VII)

with a compound of formula VIII

$$U_2 - C - D - E \qquad \text{(VIII)}$$

(wherein C, D, E and X are as defined in any one of claims 1 to 5,
one of the groups U_1 or U_2 represents an HNR_3- group, wherein R_3 is as defined in any one of claims 1 to 5, and the other group U_1 or U_2 represents a $Z_2-A'-$ group, wherein A' represents a carbonyl or sulphonyl group and Z_2 represents a hydroxy group or a nucleophilic leaving group or with a reactive derivative thereof;

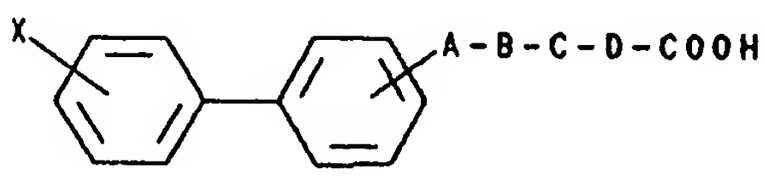
f) (to prepare compounds of formula I wherein the E-D-C group is an $HOOC-(CH_2)_n-CO-NH-$ group) hydrolysing of a compound of formula IX



(IX)

(wherein A, B, X and n are as defined in any one of claims 1 to 5);

g) (to prepare compounds of formula I wherein E represents a C_{2-6}(alkoxycarbonyl) group wherein the alkoxy moiety may be substituted in the 1-, 2- or 3-position by an aryl or pyridyl group or may be substituted in the 2- or 3-position by a pyrrolidino, piperidino, hexamethylene-imino, 2-oxo-1-pyrrolidinyl, morpholino, thiomorpholino or 1,1-dioxido-thiomorpholino group or by a piperazino group optionally substituted in the 4-position by a group R_5) reacting a compound of formula X



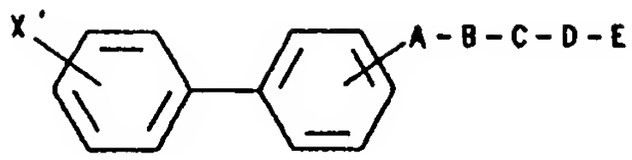
(X)

(wherein A, B, C, D and X are as defined in any one of claims 1 to 5) or a reactive derivative thereof, with a compound of formula XI

$$H - R_9 \qquad (XI)$$

(wherein R_9 represents a C_{1-5}-alkoxy group wherein the alkoxy moiety may be substituted in the 1-, 2- or 3-position by an aryl or pyridyl group or in the 2- or 3-position by a pyrrolidino, piperidino, hexamethyleneimino, 2-oxo-1-pyrrolidinyl, morpholino, thiomorpholino or 1,1-dioxido-thiomorpholino group or by a piperazino group optionally substituted in the 4-position by a group R_5);

h) (to prepare compounds of formula I wherein group X contains a cyano, alkoxycarbonyl or aralkoxycarbonyl group) reacting a compound of formula XII



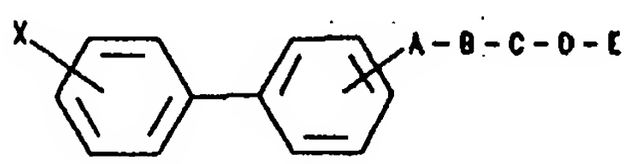
(XII)

(wherein A, B, C, D and E are as defined in any one of claims 1 to 5 and
X' represents an amino, aminoalkyl, amidino, guanidino or guanidinoalkyl group) with bromocyanogen or with an ester of formula XIII

$$Z_3 - CO - OR_3' \qquad (XIII)$$

(wherein R_3' represents an optionally phenyl-substituted C_{1-3}-alkyl group and
Z_3 represents a nucleophilic leaving group);

i) (to prepare compounds of formula I wherein A or C represents a sulphinyl or sulphonyl group or R_1 or R_2 represents an alkylsulphinyl or alkylsulphonyl group or E contains a 1-oxidothiomorpholino or 1,1-dioxidothiomorpholino group) oxidising a compound of formula XIV



(XIV)

(wherein A, B, C, D, E and X are as defined in any one of claims 1 to 5 with the proviso that A or C represents a sulphur atom or a sulphinyl group or R_1 or R_2 contains a sulphenyl or sulphinyl group or E contains a thiomorpholino or 1-oxidothiomorpholino group);

j) performing any one of steps (a) to (i) above on a compound in which reactive groups are protected by protective groups and subsequently removing the

protective groups;

k) separating stereoisomers of a compound of formula I from a mixture thereof; and

l) converting a compound of formula I into a salt thereof or converting a salt of a compound of formula I into the free compound.

11. The use of a compound of formula I as claimed in any one of claims 1 to 6 or a physiologically acceptable salt thereof for the manufacture of a therapeutic agent for use in combatting conditions in which cell aggregations or cell-matrix interactions occur.

12. A method of combatting conditions in which cell aggregations or cell-matrix interactions occur which method comprises administering to a human or non-human, preferably mammalian, subject a compound of formula I as claimed in any one of claims 1 to 6 or a physiologically acceptable salt thereof.

13. A compound as herein disclosed in any one of the Examples.

14. Each and every novel compound, composition, process, use and method as hereinbefore disclosed.

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